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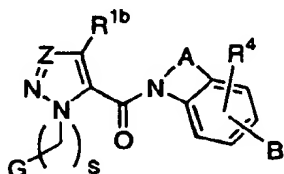
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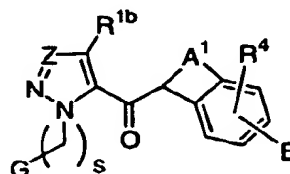
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- (71) Applicant: DU PONT PHARMACEUTICALS COMPANY [US/US]; 974 Centre Road, WR-1ST18, Wilmington, DE 19807 (US).
- (72) Inventors: JACOBSON, Irina, C.; 3205 Heathwood Road, Wilmington, DE 19810 (US). QUAN, Mimi, L.; 113 Venus Drive, Newark, DE 19711 (US).
- (74) Agent: ROPER, David, J.; Du Pont Pharmaceuticals Company, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).
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(54) Title: NITROGEN CONTAINING HETEROBICYCLES AS FACTOR Xa INHIBITORS



(A)



(B)

(57) Abstract: This invention relates generally to nitrogen containing heterobicycles of formulas A and B: which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

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## TITLE

Nitrogen Containing Heterobicycles as Factor Xa Inhibitors

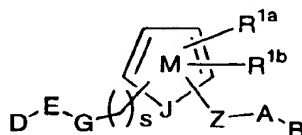
## FIELD OF THE INVENTION

10 This invention relates generally to nitrogen containing heterobicycles, which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of  
 15 thromboembolic disorders.

## BACKGROUND OF THE INVENTION

WO98/28269 describes factor Xa inhibitors of the formula:

20



wherein ring M contains, in addition to J, 0-3 N atoms, J is N or NH, and D is substituted meta or para to G on E.

However, WO98/28269 does not disclose compounds containing  
 25 heterobicycles like those of the present invention.

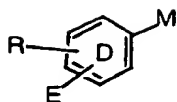
WO98/57951 describes factor Xa inhibitors of the formula:



I

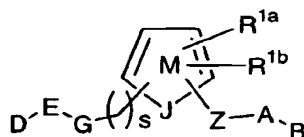
30 wherein ring D is selected from  $-\text{CH}_2\text{N}=\text{CH}-$ ,  $-\text{CH}_2\text{CH}_2\text{N}=\text{CH}-$ , a 5-6 membered aromatic system containing from 0-2 heteroatoms selected from the group N, O, and S, ring E contains 0-2 N atom and M is a variety of rings including pyrazole and triazole. WO98/57951 does not, however, disclose compounds  
 35 containing heterobicycles like those of the present invention.

WO98/57937 describes factor Xa inhibitors of the formula:



wherein ring D is phenyl or pyridyl and M is a variety of rings including pyrazole and triazole. However, WO98/57937 does not disclose compounds containing heterobicycles like those of the present invention.

PCT/US98/26427 describes factor Xa inhibitors of the formula:



wherein ring M contains, in addition to J, 0-3 N atoms and J is N or NH and D is substituted ortho to G on E. However, PCT/US98/26427 does not disclose compounds containing heterobicycles like those of the present invention.

Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V,  $\text{Ca}^{2+}$  and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin (Elodi, S., Varadi, K.: Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of the complex in the amplification of blood coagulation. *Thromb. Res.* **1979**, 15, 617-629), inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system.

Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors.

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## SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel nitrogen containing heterobicycles which are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

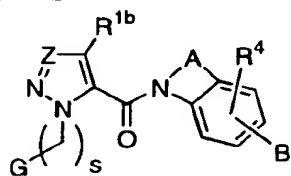
It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

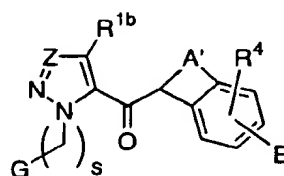
It is another object of the present invention to provide novel bicyclic compounds for use in therapy.

It is another object of the present invention to provide the use of novel bicyclic compounds for the manufacture of a medicament for the treatment of a thromboembolic disorder.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of Formulas A and B



A

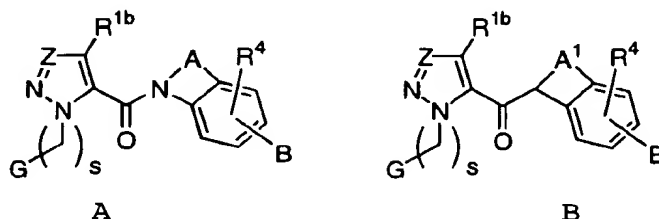


B

or pharmaceutically acceptable salt or prodrug forms thereof, are effective factor Xa inhibitors.

## 5 DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

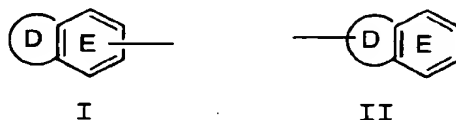
[1] Thus, in an embodiment, the present invention provides a novel compound of formula A or B:



10

or a stereoisomer or pharmaceutically acceptable salt thereof;

15 G is a group of formula I or II:



20 ring D is selected from  $-(CH_2)_3-$ ,  $-(CH_2)_4-$ ,  $-CH_2N=CH-$ ,  $-CH_2CH_2N=CH-$ , and a 5-6 membered aromatic system containing from 0-2 heteroatoms selected from the group N, O, and S;

25 ring D, when present, is substituted with 0-2 R, provided that when ring D is unsubstituted, it contains at least one heteroatom;

30 E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, substituted with 0-1 R;

R is selected from Cl, F, Br, I, OH,  $C_{1-3}$  alkoxy,  $NH_2$ ,  $NH(C_{1-3} \text{ alkyl})$ ,  $N(C_{1-3} \text{ alkyl})_2$ ,  $CH_2NH_2$ ,  $CH_2NH(C_{1-3} \text{ alkyl})$ ,  $CH_2N(C_{1-3} \text{ alkyl})_2$ ,  $CH_2CH_2NH_2$ ,  $CH_2CH_2NH(C_{1-3} \text{ alkyl})$ , and  $CH_2CH_2N(C_{1-3} \text{ alkyl})_2$ ;

35

alternatively, ring D is absent;

- 5 when ring D is absent, ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and ring E is substituted with R<sup>a</sup> and R<sup>b</sup>;
- 10 R<sup>a</sup> is selected from H, F, Cl, Br, I, SR<sup>3</sup>, CO<sub>2</sub>R<sup>3</sup>, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>t</sub>OR<sup>3</sup>, C<sub>1-4</sub> alkyl, OCF<sub>3</sub>, CF<sub>3</sub>, C(O)NR<sup>7</sup>R<sup>8</sup>, and (CR<sup>8</sup>R<sup>9</sup>)<sub>t</sub>NR<sup>7</sup>R<sup>8</sup>;
- 15 R<sup>b</sup> is selected from F, Cl, Br, I, OH, C<sub>1-3</sub> alkoxy, CN, C(=NR<sup>8</sup>)NR<sup>7</sup>R<sup>9</sup>, NHC(=NR<sup>8</sup>)NR<sup>7</sup>R<sup>9</sup>, NR<sup>8</sup>CH(=NR<sup>7</sup>), C(O)NR<sup>7</sup>R<sup>8</sup>, (CR<sup>8</sup>R<sup>9</sup>)<sub>t</sub>NR<sup>7</sup>R<sup>8</sup>, SH, C<sub>1-3</sub> alkyl-S, S(O)R<sup>3b</sup>, S(O)<sub>2</sub>R<sup>3a</sup>, S(O)<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, OCF<sub>3</sub>, and a 5-6 membered heteroaromatic system containing from 1-4 heteroatoms selected from the group N, O, and S and substituted with R<sup>c</sup>;
- 20 alternatively, R<sup>a</sup> and R<sup>b</sup> combine to form methylenedioxy or ethylenedioxy;
- 25 R<sup>c</sup> is selected from OH, SH, C<sub>1-3</sub> alkoxy, C<sub>1-3</sub> thioalkoxy, NH<sub>2</sub>, NH(C<sub>1-3</sub> alkyl), N(C<sub>1-3</sub> alkyl)<sub>2</sub>, CH<sub>2</sub>NH<sub>2</sub>, CH<sub>2</sub>NH(C<sub>1-3</sub> alkyl), CH<sub>2</sub>N(C<sub>1-3</sub> alkyl)<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>NH(C<sub>1-3</sub> alkyl), and CH<sub>2</sub>CH<sub>2</sub>N(C<sub>1-3</sub> alkyl)<sub>2</sub>;
- 30 Z is N or CR<sup>1a</sup>;
- R<sup>1a</sup> is absent or selected from -(CH<sub>2</sub>)<sub>r</sub>-R<sup>1c</sup>, -CH=CH-R<sup>1c</sup>, NCH<sub>2</sub>R<sup>1d</sup>, OCH<sub>2</sub>R<sup>1d</sup>, SCH<sub>2</sub>R<sup>1d</sup>, NH(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1c</sup>, O(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1c</sup>, and S(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1c</sup>;
- 35 R<sup>1b</sup> is absent or selected from -(CH<sub>2</sub>)<sub>r</sub>-R<sup>1c</sup>, -CH=CH-R<sup>1c</sup>, NCH<sub>2</sub>R<sup>1d</sup>, OCH<sub>2</sub>R<sup>1d</sup>, SCH<sub>2</sub>R<sup>1d</sup>, NH(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1c</sup>, O(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1c</sup>, and S(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1c</sup>;
- 40 alternatively, R<sup>1a</sup> and R<sup>1b</sup>, when both are present, together with the atoms to which they are attached form a 5-8 membered saturated, partially saturated or unsaturated

5 ring substituted with 0-2  $R^4$  and which contains from  
0-2 heteroatoms selected from the group consisting of  
N, O, and S;

10  $R^{1c}$  is selected from H,  $C_{1-3}$  alkyl, F, Cl, Br, I, -CN, -CHO,  
( $CF_2$ ) $_r$ CF $_3$ , ( $CH_2$ ) $_r$ OR $^2$ , NR $^2$ R $^{2a}$ , C(O)R $^{2c}$ , OC(O)R $^2$ ,  
( $CF_2$ ) $_r$ CO $_2$ R $^{2c}$ , S(O) $_p$ R $^{2b}$ , NR $^2$ (CH $_2$ ) $_r$ OR $^2$ , CH(=NR $^{2c}$ )NR $^2$ R $^{2a}$ ,  
NR $^2$ C(O)R $^{2b}$ , NR $^2$ C(O)NHR $^{2b}$ , NR $^2$ C(O) $_2$ R $^{2a}$ , OC(O)NR $^{2a}$ R $^{2b}$ ,  
C(O)NR $^2$ R $^{2a}$ , C(O)NR $^2$ (CH $_2$ ) $_r$ OR $^2$ , SO $_2$ NR $^2$ R $^{2a}$ , NR $^2$ SO $_2$ R $^{2b}$ ,  $C_{3-6}$   
15 carbocyclic residue substituted with 0-2  $R^4$ , and 5-10  
membered heterocyclic system containing from 1-4  
heteroatoms selected from the group consisting of N, O,  
and S substituted with 0-2  $R^4$ ;

20  $R^{1d}$  is selected from H, CH(CH $_2$ OR $^2$ ) $_2$ , C(O)R $^{2c}$ , C(O)NR $^2$ R $^{2a}$ ,  
S(O)R $^{2b}$ , S(O) $_2$ R $^{2b}$ , and SO $_2$ NR $^2$ R $^{2a}$ ;

$R^2$ , at each occurrence, is selected from H, CF $_3$ ,  $C_{1-6}$  alkyl,  
benzyl,  $C_{3-6}$  carbocyclic residue substituted with 0-2  
25  $R^{4b}$ , a  $C_{3-6}$  carbocyclic-CH $_2$ - residue substituted with  
0-2  $R^{4b}$ , and 5-6 membered heterocyclic system containing  
from 1-4 heteroatoms selected from the group consisting  
of N, O, and S substituted with 0-2  $R^{4b}$ ;

30  $R^{2a}$ , at each occurrence, is selected from H, CF $_3$ ,  $C_{1-6}$  alkyl,  
benzyl,  $C_{3-6}$  carbocyclic residue substituted with 0-2  
 $R^{4b}$ , and 5-6 membered heterocyclic system containing  
from 1-4 heteroatoms selected from the group consisting  
of N, O, and S substituted with 0-2  $R^{4b}$ ;

35  $R^{2b}$ , at each occurrence, is selected from CF $_3$ ,  $C_{1-4}$  alkoxy,  
 $C_{1-6}$  alkyl, benzyl,  $C_{3-6}$  carbocyclic residue substituted  
with 0-2  $R^{4b}$ , and 5-6 membered heterocyclic system  
containing from 1-4 heteroatoms selected from the group  
consisting of N, O, and S substituted with 0-2  $R^{4b}$ ;

40

5 R<sup>2c</sup>, at each occurrence, is selected from CF<sub>3</sub>, OH, C<sub>1-4</sub>  
alkoxy, C<sub>1-6</sub> alkyl, benzyl, C<sub>3-6</sub> carbocyclic residue  
substituted with 0-2 R<sup>4b</sup>, and 5-6 membered heterocyclic  
system containing from 1-4 heteroatoms selected from  
10 the group consisting of N, O, and S substituted with  
0-2 R<sup>4b</sup>;

alternatively, R<sup>2</sup> and R<sup>2a</sup>, together with the atom to which  
they are attached, combine to form a 5 or 6 membered  
saturated, partially saturated or unsaturated ring  
15 substituted with 0-2 R<sup>4b</sup> and containing from 0-1  
additional heteroatoms selected from the group  
consisting of N, O, and S;

R<sup>3</sup>, at each occurrence, is selected from H, C<sub>1-4</sub> alkyl, and  
20 phenyl;

R<sup>3a</sup>, at each occurrence, is selected from H, C<sub>1-4</sub> alkyl, and  
phenyl;

25 R<sup>3b</sup>, at each occurrence, is selected from H, C<sub>1-4</sub> alkyl, and  
phenyl;

R<sup>3c</sup>, at each occurrence, is selected from C<sub>1-4</sub> alkyl, and  
phenyl;

30 A is 2-5 membered linker substituted with 0-2 R<sup>4</sup> and  
selected from C<sub>2-4</sub> alkylene, C<sub>2-4</sub> alkenylene,  
(CH<sub>2</sub>)<sub>u</sub>O(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>NH(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>C(O)(CH<sub>2</sub>)<sub>u</sub>,  
(CH<sub>2</sub>)<sub>u</sub>C(O)O(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>OC(O)(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>C(O)NH(CH<sub>2</sub>)<sub>u</sub>,  
35 (CH<sub>2</sub>)<sub>u</sub>NHC(O)(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>S(O)<sub>p</sub>(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>SO<sub>2</sub>NH(CH<sub>2</sub>)<sub>u</sub>,  
and (CH<sub>2</sub>)<sub>u</sub>NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>u</sub>, provided that A forms other than  
a N-O or N-S bond;

A<sup>1</sup> is 2-5 membered linker substituted with 0-2 R<sup>4</sup> and  
40 selected from C<sub>2-4</sub> alkylene, C<sub>2-4</sub> alkenylene,  
(CH<sub>2</sub>)<sub>u</sub>O(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>NH(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>C(O)(CH<sub>2</sub>)<sub>u</sub>,



- 5 (CH<sub>2</sub>)<sub>u</sub>C(O)O(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>OC(O)(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>C(O)NH(CH<sub>2</sub>)<sub>u</sub>,  
 (CH<sub>2</sub>)<sub>u</sub>NHC(O)(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>S(O)<sub>p</sub>(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>SO<sub>2</sub>NH(CH<sub>2</sub>)<sub>u</sub>,  
 and (CH<sub>2</sub>)<sub>u</sub>NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>u</sub>, provided that A<sup>1</sup> forms other than  
 a N-O or N-S bond;
- 10 alternatively, the CH<sub>2</sub>-A<sup>1</sup> group is replaced by a group  
 selected from C=CH-NH, C=CH-O, and C=CH-S;
- B is selected from:  
 X-Y, NR<sup>2</sup>R<sup>2a</sup>, C(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>C(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>,  
 15 C<sub>3-10</sub> carbocyclic residue substituted with 0-2 R<sup>4a</sup>, and  
 5-10 membered heterocyclic system containing from 1-4  
 heteroatoms selected from the group consisting of N, O, and  
 S substituted with 0-2 R<sup>4a</sup>;
- 20 X is selected from C<sub>1-4</sub> alkylene, -CR<sup>2</sup>(CR<sup>2</sup>R<sup>2b</sup>)(CH<sub>2</sub>)<sub>t</sub>-, -C(O)-,  
 -C(=NR<sup>1d</sup>)-, -CR<sup>2</sup>(NR<sup>1d</sup>R<sup>2</sup>)-, -CR<sup>2</sup>(OR<sup>2</sup>)-, -CR<sup>2</sup>(SR<sup>2</sup>)-,  
 -C(O)CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>C(O)-, -S(O)<sub>p</sub>-, -S(O)<sub>p</sub>CR<sup>2</sup>R<sup>2a</sup>-,  
 -CR<sup>2</sup>R<sup>2a</sup>S(O)<sub>p</sub>-, -S(O)<sub>2</sub>NR<sup>2</sup>-, -NR<sup>2</sup>S(O)<sub>2</sub>-, -NR<sup>2</sup>S(O)<sub>2</sub>CR<sup>2</sup>R<sup>2a</sup>-,  
 -CR<sup>2</sup>R<sup>2a</sup>S(O)<sub>2</sub>NR<sup>2</sup>-, -NR<sup>2</sup>S(O)<sub>2</sub>NR<sup>2</sup>-, -C(O)NR<sup>2</sup>-, -NR<sup>2</sup>C(O)-,  
 25 -C(O)NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -NR<sup>2</sup>C(O)CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>C(O)NR<sup>2</sup>-,  
 -CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>C(O)-, -NR<sup>2</sup>C(O)O-, -OC(O)NR<sup>2</sup>-, -NR<sup>2</sup>C(O)NR<sup>2</sup>-,  
 -NR<sup>2</sup>-, -NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>-, O, -CR<sup>2</sup>R<sup>2a</sup>O-, and  
 -OCR<sup>2</sup>R<sup>2a</sup>-;
- 30 Y is selected from:  
 (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, provided that X-Y do not form a N-N, O-N,  
 or S-N bond,  
 C<sub>3-10</sub> carbocyclic residue substituted with 0-2 R<sup>4a</sup>, and  
 5-10 membered heterocyclic system containing from 1-4  
 35 heteroatoms selected from the group consisting of N, O, and  
 S substituted with 0-2 R<sup>4a</sup>;
- R<sup>4</sup>, at each occurrence, is selected from H, =O, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, F,  
 Cl, Br, I, C<sub>1-4</sub> alkyl, -CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>,  
 40 (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>2c</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>C(O)NR<sup>2</sup>R<sup>2a</sup>,  
 CH(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, CH(=NS(O)<sub>2</sub>R<sup>5</sup>)NR<sup>2</sup>R<sup>2a</sup>, NHC(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>,

- 5 C(O)NHC(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>-C<sub>1-4</sub> alkyl, NR<sup>2</sup>SO<sub>2</sub>R<sup>5</sup>, S(O)<sub>p</sub>R<sup>5</sup>, (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>, NCH<sub>2</sub>R<sup>1d</sup>, OCH<sub>2</sub>R<sup>1d</sup>, SCH<sub>2</sub>R<sup>1d</sup>, N(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1c</sup>, O(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1c</sup>, and S(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1c</sup>;
- 10 R<sup>4'</sup>, at each occurrence, is selected from H, =O, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, F, Cl, Br, I, C<sub>1-4</sub> alkyl, -CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>2c</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;
- 15 R<sup>4a</sup>, at each occurrence, is selected from H, =O, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, (CH<sub>2</sub>)<sub>r</sub>-F, (CH<sub>2</sub>)<sub>r</sub>-Br, (CH<sub>2</sub>)<sub>r</sub>-Cl, Cl, Br, F, I, C<sub>1-4</sub> alkyl, -CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>2c</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, C(O)NH(CH<sub>2</sub>)<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>C(O)NR<sup>2</sup>R<sup>2a</sup>, CH(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, NHC(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>,  
 20 NR<sup>2</sup>SO<sub>2</sub>-C<sub>1-4</sub> alkyl, C(O)NHSO<sub>2</sub>-C<sub>1-4</sub> alkyl, NR<sup>2</sup>SO<sub>2</sub>R<sup>5</sup>, S(O)<sub>p</sub>R<sup>5</sup>, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;
- alternatively, one R<sup>4a</sup> is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-1 R<sup>5</sup>;
- 25 R<sup>4b</sup>, at each occurrence, is selected from H, =O, (CH<sub>2</sub>)<sub>r</sub>OR<sup>3</sup>, F, Cl, Br, I, C<sub>1-4</sub> alkyl, -CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>3</sup>R<sup>3a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>3</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)OR<sup>3c</sup>, NR<sup>3</sup>C(O)R<sup>3a</sup>, C(O)NR<sup>3</sup>R<sup>3a</sup>,  
 30 NR<sup>3</sup>C(O)NR<sup>3</sup>R<sup>3a</sup>, CH(=NR<sup>3</sup>)NR<sup>3</sup>R<sup>3a</sup>, NR<sup>3</sup>C(=NR<sup>3</sup>)NR<sup>3</sup>R<sup>3a</sup>, SO<sub>2</sub>NR<sup>3</sup>R<sup>3a</sup>, NR<sup>3</sup>SO<sub>2</sub>NR<sup>3</sup>R<sup>3a</sup>, NR<sup>3</sup>SO<sub>2</sub>-C<sub>1-4</sub> alkyl, NR<sup>3</sup>SO<sub>2</sub>CF<sub>3</sub>, NR<sup>3</sup>SO<sub>2</sub>-phenyl, S(O)<sub>p</sub>CF<sub>3</sub>, S(O)<sub>p</sub>-C<sub>1-4</sub> alkyl, S(O)<sub>p</sub>-phenyl, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;
- 35 R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-6</sub> alkyl, phenyl substituted with 0-2 R<sup>6</sup>, and benzyl substituted with 0-2 R<sup>6</sup>;
- 40 R<sup>6</sup>, at each occurrence, is selected from H, OH, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, halo, C<sub>1-4</sub> alkyl, CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>2b</sup>,

5            $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$ ,  $\text{NR}^2\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$ ,  $\text{CH}(=\text{NH})\text{NH}_2$ ,  $\text{NHC}(=\text{NH})\text{NH}_2$ ,  
           $\text{SO}_2\text{NR}^2\text{R}^{2a}$ ,  $\text{NR}^2\text{SO}_2\text{NR}^2\text{R}^{2a}$ , and  $\text{NR}^2\text{SO}_2\text{C}_{1-4}$  alkyl;

$\text{R}^7$ , at each occurrence, is selected from H, OH,  $\text{C}_{1-6}$  alkyl,  
           $\text{C}_{1-6}$  alkylcarbonyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{1-4}$  alkoxy carbonyl,  
10        $(\text{CH}_2)_n$ -phenyl,  $\text{C}_{6-10}$  aryloxy,  $\text{C}_{6-10}$  aryloxy carbonyl,  $\text{C}_{6-10}$   
          arylmethylcarbonyl,  $\text{C}_{1-4}$  alkylcarbonyloxy  $\text{C}_{1-4}$   
          alkoxy carbonyl,  $\text{C}_{6-10}$  arylcarbonyloxy  $\text{C}_{1-4}$   
          alkoxy carbonyl,  $\text{C}_{1-6}$  alkylaminocarbonyl,  
          phenylaminocarbonyl, and phenyl  $\text{C}_{1-4}$  alkoxy carbonyl;

15        $\text{R}^8$ , at each occurrence, is selected from H,  $\text{C}_{1-6}$  alkyl and  
           $(\text{CH}_2)_n$ -phenyl;

          alternatively,  $\text{R}^7$  and  $\text{R}^8$  combine to form a 5 or 6 membered  
20       saturated, ring which contains from 0-1 additional  
          heteroatoms selected from the group consisting of N, O,  
          and S;

$\text{R}^9$ , at each occurrence, is selected from H,  $\text{C}_{1-6}$  alkyl and  
25        $(\text{CH}_2)_n$ -phenyl;

          n, at each occurrence, is selected from 0, 1, 2, and 3;

          m, at each occurrence, is selected from 0, 1, and 2;

30       p, at each occurrence, is selected from 0, 1, and 2;

          r, at each occurrence, is selected from 0, 1, 2, and 3;

35       s, at each occurrence, is selected from 0, 1, and 2;

          t, at each occurrence, is selected from 0, 1, 2, and 3; and,

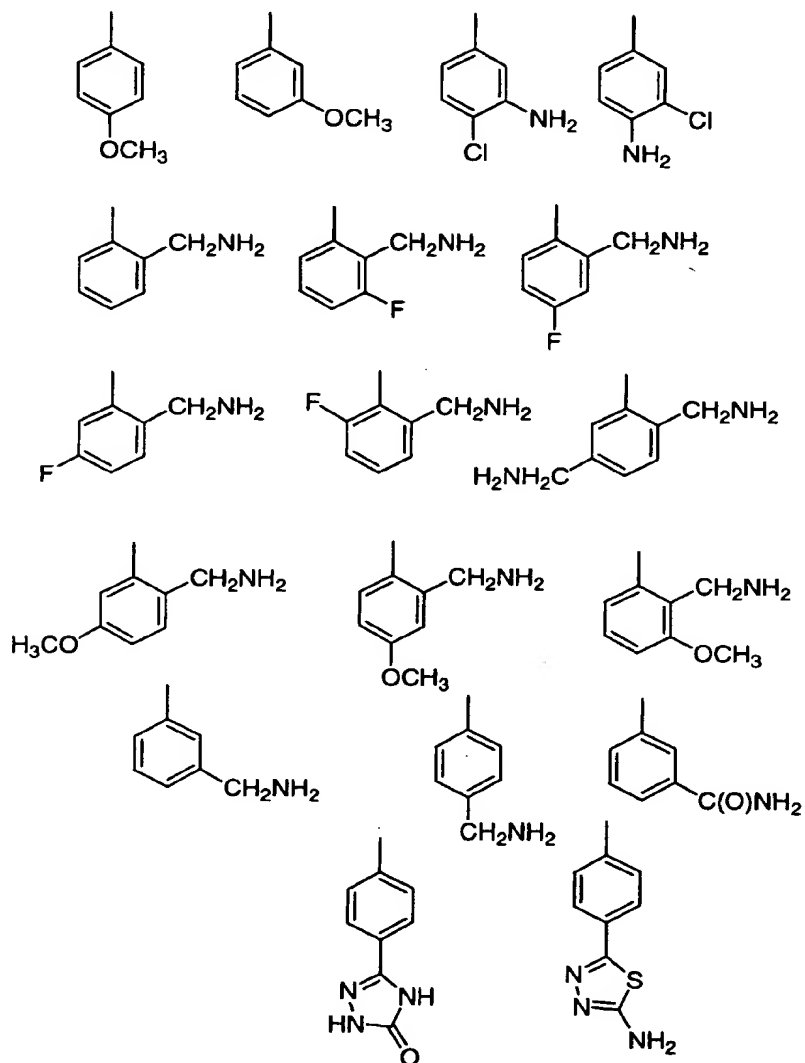
          u, at each occurrence, is selected from 0, 1, 2, and 3.

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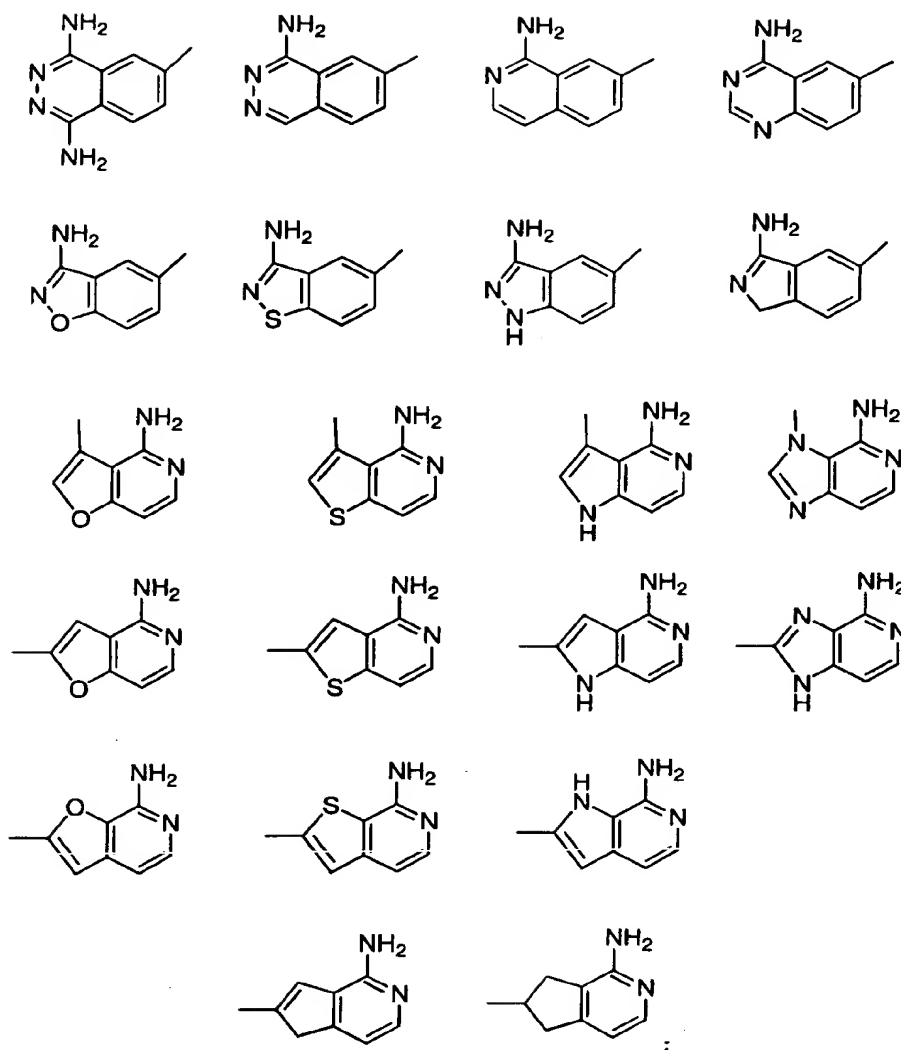
5 [2] In a preferred embodiment, the present invention provides a novel compound, wherein the compound is selected from the group:

G is selected from the group:

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A is 3-5 membered linker substituted with 0-2  $R^4$  and selected from  $C_{2-4}$  alkylene,  $(CH_2)_uO(CH_2)_u$ ,  $(CH_2)_uNH(CH_2)_u$ ,  $(CH_2)_uC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)O(CH_2)_u$ ,  $(CH_2)_uOC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)NH(CH_2)_u$ ,  $(CH_2)_uNHC(O)(CH_2)_u$ ,  $(CH_2)_uS(O)_p(CH_2)_u$ ,  $(CH_2)_uSO_2NH(CH_2)_u$ , and  $(CH_2)_uNHSO_2(CH_2)_u$ , provided that A forms other than a N-O or N-S bond;

20

$A^1$  is 3-5 membered linker substituted with 0-2  $R^4$  and selected from  $C_{2-4}$  alkylene,  $(CH_2)_uO(CH_2)_u$ ,  $(CH_2)_uNH(CH_2)_u$ ,  $(CH_2)_uC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)O(CH_2)_u$ ,  $(CH_2)_uOC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)NH(CH_2)_u$ ,

5 (CH<sub>2</sub>)<sub>u</sub>NHC(O)(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>S(O)<sub>p</sub>(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>SO<sub>2</sub>NH(CH<sub>2</sub>)<sub>u</sub>,  
and (CH<sub>2</sub>)<sub>u</sub>NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>u</sub>, provided that A<sup>1</sup> forms other than  
a N-O or N-S bond;

alternatively, the CH<sub>2</sub>-A<sup>1</sup> group is replaced by a group  
10 selected from C=CH-NH and C=CH-O;

B is selected from: H, Y, X-Y;

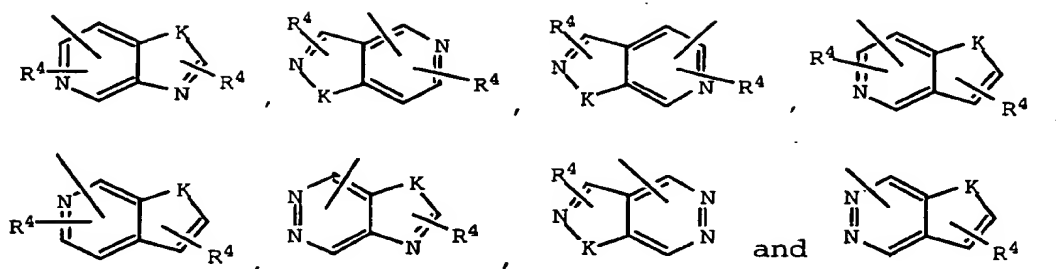
X is selected from C<sub>1-4</sub> alkylene, -C(O)-, -C(=NR)-,  
15 -CR<sup>2</sup>(NR<sup>2</sup>R<sup>2a</sup>)-, -C(O)CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>C(O)-, -C(O)NR<sup>2</sup>-,  
-NR<sup>2</sup>C(O)-, -C(O)NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -NR<sup>2</sup>C(O)CR<sup>2</sup>R<sup>2a</sup>-,  
-CR<sup>2</sup>R<sup>2a</sup>C(O)NR<sup>2</sup>-, -CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>C(O)-, -NR<sup>2</sup>C(O)NR<sup>2</sup>-, -NR<sup>2</sup>-,  
-NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>-, O, -CR<sup>2</sup>R<sup>2a</sup>O-, and -OCR<sup>2</sup>R<sup>2a</sup>-;

20 Y is NR<sup>2</sup>R<sup>2a</sup>, provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following  
carbocyclic and heterocyclic systems which are  
substituted with 0-2 R<sup>4a</sup>;

25 cyclopropyl, cyclopentyl, cyclohexyl, phenyl,  
piperidiny, piperazinyl, pyridyl, pyrimidyl, furanyl,  
morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl,  
oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl,  
isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,  
30 thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,  
1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl,  
1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl,  
1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl,  
1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,  
35 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl,  
benzothiofuranyl, indolyl, benzimidazolyl,  
benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl,  
benzisothiazolyl, and isoindazolyl;

40 alternatively, Y is selected from the following bicyclic  
heteroaryl ring systems:



K is selected from O, S, NH, and N; and,

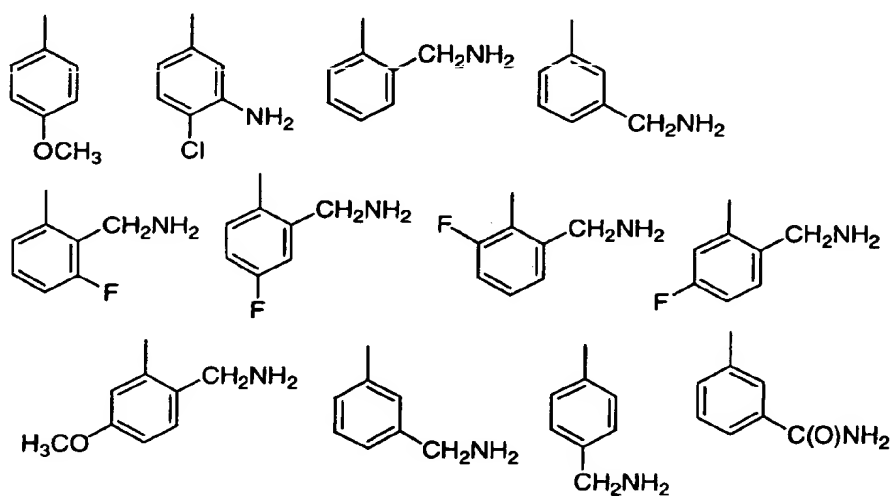
s is 0.

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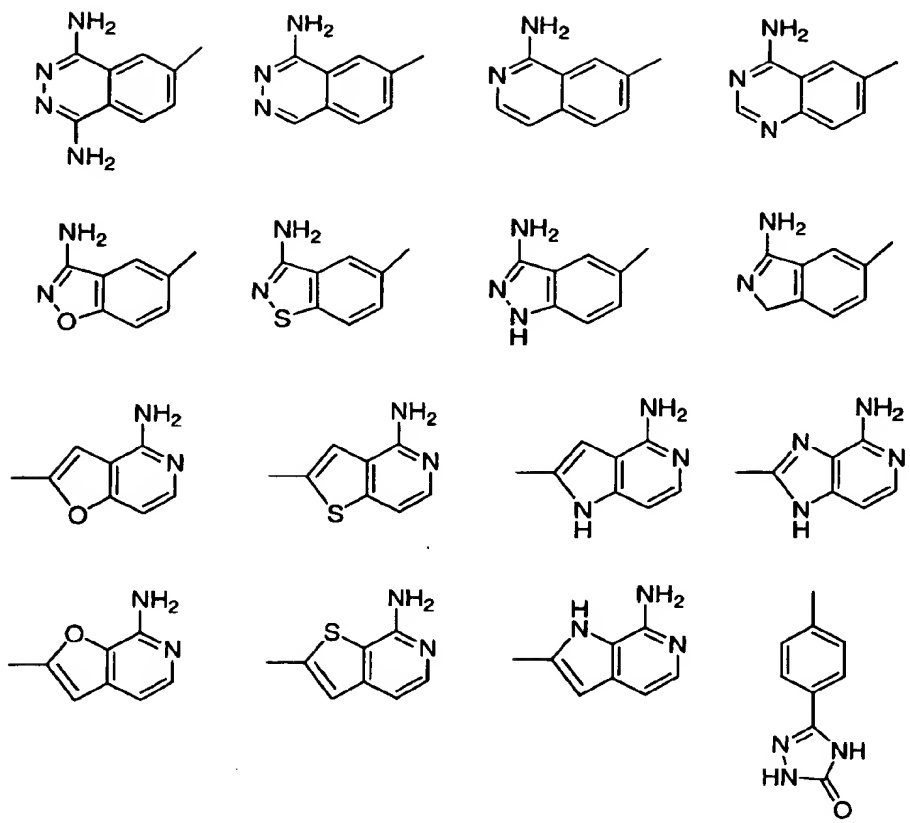
[3] In a more preferred embodiment, the present invention provides a novel compound, wherein the compound is selected from the group:

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G is selected from the group:



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10 A is 3-5 membered linker substituted with 0-2  $R^4$  and  
 selected from  $C_{2-4}$  alkylene,  $(CH_2)_uO(CH_2)_u$ ,  
 $(CH_2)_uNH(CH_2)_u$ ,  $(CH_2)_uC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)O(CH_2)_u$ ,  
 $(CH_2)_uOC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)NH(CH_2)_u$ ,  
 $(CH_2)_uNHC(O)(CH_2)_u$ ,  $(CH_2)_uSO_2NH(CH_2)_u$ , and  
 $(CH_2)_uNHSO_2(CH_2)_u$ , provided that A forms other than a N-  
 15 O or N-S bond;

A<sup>1</sup> is 3-5 membered linker substituted with 0-2  $R^4$  and  
 selected from  $C_{2-4}$  alkylene,  $(CH_2)_uO(CH_2)_u$ ,  
 $(CH_2)_uNH(CH_2)_u$ ,  $(CH_2)_uC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)NH(CH_2)_u$ ,  
 20  $(CH_2)_uNHC(O)(CH_2)_u$ ,  $(CH_2)_uSO_2NH(CH_2)_u$ , and  
 $(CH_2)_uNHSO_2(CH_2)_u$ , provided that A<sup>1</sup> forms other than a N-  
 O or N-S bond; and

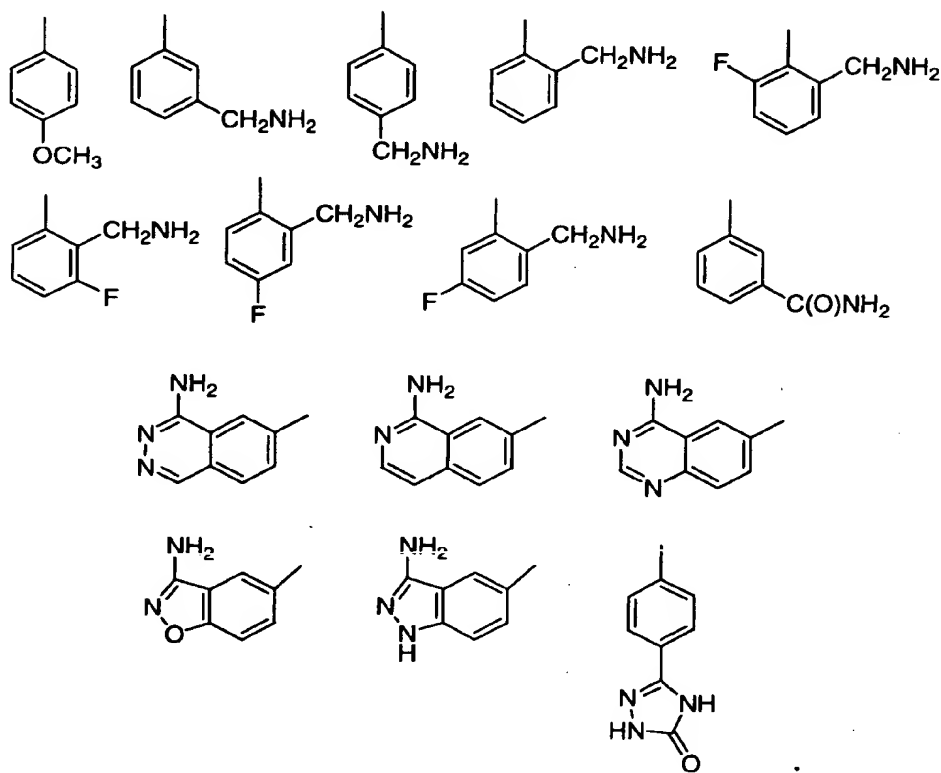
alternatively, the  $CH_2$ -A<sup>1</sup> group is replaced by a group  
 25 selected from  $C=CH-NH$  and  $C=CH-O$ .



5

[4] In an even more preferred embodiment, the present invention provides a novel compound, wherein:

10 G is selected from:



15

A is 3-5 membered linker substituted with 0-2  $R^4$  and selected from  $C_{2-4}$  alkylene,  $(CH_2)_uO(CH_2)_u$ ,  $(CH_2)_uNH(CH_2)_u$ ,  $(CH_2)_uC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)O(CH_2)_u$ , and  $(CH_2)_uOC(O)(CH_2)_u$ , provided that A forms other than a N-O or N-S bond;

20

$A^1$  is 3-5 membered linker substituted with 0-2  $R^4$  and selected from  $C_{2-4}$  alkylene,  $(CH_2)_uO(CH_2)_u$ ,  $(CH_2)_uNH(CH_2)_u$ ,  $(CH_2)_uC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)NH(CH_2)_u$ ,  $(CH_2)_uNHC(O)(CH_2)_u$ ,  $(CH_2)_uSO_2NH(CH_2)_u$ , and

25

5 (CH<sub>2</sub>)<sub>u</sub>NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>u</sub>, provided that A<sup>1</sup> forms other than a N-O or N-S bond; and

alternatively, the CH<sub>2</sub>-A<sup>1</sup> group is replaced by a group  
selected from C=CH-NH and C=CH-O.

10

[5] In a still more preferred embodiment, the present invention provides a novel compound, wherein;

15 B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R<sup>4a</sup>;

R<sup>2</sup>, at each occurrence, is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>,  
20 cyclopropylmethyl, cyclobutyl, and cyclopentyl;

R<sup>2a</sup>, at each occurrence, is H or CH<sub>3</sub>;

alternatively, R<sup>2</sup> and R<sup>2a</sup>, together with the atom to which  
25 they are attached, combine to form pyrrolidine substituted with 0-2 R<sup>4b</sup>;

R<sup>4</sup>, at each occurrence, is selected from OH, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, halo, C<sub>1-4</sub> alkyl, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;

30

R<sup>4a</sup> is selected from C<sub>1-4</sub> alkyl, CF<sub>3</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, S(O)<sub>p</sub>R<sup>5</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, and 1-CF<sub>3</sub>-tetrazol-2-yl;

R<sup>4b</sup>, at each occurrence, is selected from H, CH<sub>3</sub>, and OH;

35

R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-6</sub> alkyl, phenyl, and benzyl;

40 A is 3-5 membered linker substituted with 0-2 R<sup>4</sup> and selected from C<sub>2-4</sub> alkylene, (CH<sub>2</sub>)<sub>u</sub>O(CH<sub>2</sub>)<sub>u</sub>,

5 (CH<sub>2</sub>)<sub>u</sub>NH(CH<sub>2</sub>)<sub>u</sub>, and (CH<sub>2</sub>)<sub>u</sub>C(O)(CH<sub>2</sub>)<sub>u</sub>, provided that A forms other than a N-O or N-S bond;

A<sup>1</sup> is 3-5 membered linker substituted with 0-2 R<sup>4</sup> and selected from C<sub>2-4</sub> alkylene, (CH<sub>2</sub>)<sub>u</sub>O(CH<sub>2</sub>)<sub>u</sub>,  
10 (CH<sub>2</sub>)<sub>u</sub>NH(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>C(O)(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>C(O)NH(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>NHC(O)(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>SO<sub>2</sub>NH(CH<sub>2</sub>)<sub>u</sub>, and (CH<sub>2</sub>)<sub>u</sub>NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>u</sub>, provided that A<sup>1</sup> forms other than a N-O or N-S bond; and

15 alternatively, the CH<sub>2</sub>-A<sup>1</sup> group is replaced by a group selected from C=CH-NH and C=CH-O.

X is CH<sub>2</sub> or C(O);

20 Y is selected from pyrrolidino and morpholino; and, r, at each occurrence, is selected from 0, 1, and 2.

25 [6] In a further preferred embodiment, the present invention provides a novel compound, wherein;

B is selected from the group: 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-dimethylaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 2-(dimethylaminomethyl)-1-imidazolyl, 2-(N-(cyclopropylmethyl)aminomethyl)phenyl,  
30 2-(N-(cyclobutyl)aminomethyl)phenyl, 2-(N-(cyclopentyl)aminomethyl)phenyl, and 2-(N-(3-hydroxypyrrolidinyl)methyl)phenyl.

40 [7] In an even further preferred embodiment, the present invention provides a novel compound selected from:

- 5 1-[[1-[3-(Aminomethyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole;
- 10 1-[[1-[3-(Aminoiminomethyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole;
- 15 1-[[1-[3-Cyano-4-fluorophenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole;
- 20 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole;
- 25 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[2-(methylsulfonyl)phenyl]-1H-indole;
- 30 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[3-(1-pyrrolidinylmethyl)phenyl]-1H-indole;
- 35 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[(2'-dimethylaminomethyl)imidazol-1-yl]-indoline;
- 40 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3,4,5-tetrahydro-7-[2-(aminosulfonyl)phenyl]-benzazepine;
- 45 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-6-[2-(methylsulfonyl)phenyl]-1H-quinolin-4-one;
- 50 4-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-7-[2-(methylsulfonyl)phenyl]-2H-1,4-benzoxazine;
- 55 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-4-[2-(methylsulfonyl)phenyl]-3-indole;
- 60 5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1-[[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-1H-indole;

- 5 5-[2-(aminosulfonyl)phenyl]-1-[[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-1H-indole;
- 10 1-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-6-[2-(aminosulfonyl)phenyl]-2,3-dihydro-4(1H)-quinolinone;
- 15 1-[[1-[3-(aminomethyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-(1-pyrrolidinylcarbonyl)-1H-indole;
- 20 1-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-6-[2-(aminosulfonyl)phenyl]-1,2,3,4-tetrahydroquinoxaline;
- 25 1-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-7-[2-(aminosulfonyl)phenyl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine;
- 30 1-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-7-[2-(aminosulfonyl)phenyl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine;
- 35 5-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-8-[2-(aminosulfonyl)phenyl]-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one;
- 40 5-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-8-[2-(aminosulfonyl)phenyl]-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one;
- 45 1-[[1-[3-(aminoiminomethyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole;
- 50 [1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl][6-[2-[(dimethylamino)methyl]phenyl]-2,3-dihydro-1-methyl-1H-indol-3-yl]methanone;
- 55 5-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-8-[2-(aminosulfonyl)phenyl]-2,3,4,5-tetrahydro-1,5-benzoxazepine;
- 60 1-[[1-[3-(aminoiminomethyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[2-(methylsulfonyl)phenyl]-1H-indole;
- [1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl][6-[2-[(dimethylamino)methyl]phenyl]-2,3-dihydro-1H-indol-3-yl]methanone;

- 5 1-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-7-[2-(aminosulfonyl)phenyl]-  
1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one;
- 10 1-[[1-[3-(aminoiminomethyl)phenyl]-3-(trifluoromethyl)-1H-  
pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[2-(1-  
pyrrolidinylmethyl)phenyl]-1H-indole;
- 15 [1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-  
pyrazol-5-yl][2,3-dihydro-6-[2-(methylsulfonyl)phenyl]-  
1H-indol-3-yl]methanone;
- 20 1-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-7-[2-(aminosulfonyl)phenyl]-  
1,2,3,5-tetrahydro-4,1-benzoxazepine;
- 25 1-[[1-[3-(aminoiminomethyl)phenyl]-3-(trifluoromethyl)-1H-  
pyrazol-5-yl]carbonyl]-5-[2-  
[(dimethylamino)methyl]phenyl]-2,3-dihydro-1H-indole;
- 30 1-[[1-(1-amino-7-isoquinolinyl)-3-(trifluoromethyl)-1H-  
pyrazol-5-yl]carbonyl]-5-[2-  
[(dimethylamino)methyl]phenyl]-2,3-dihydro-1H-indole;
- 35 [1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-  
pyrazol-5-yl][6-[2-[(dimethylamino)methyl]phenyl]-1H-  
indol-3-yl]methanone;
- 40 [1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-  
pyrazol-5-yl][6-[2-[(dimethylamino)methyl]phenyl]-1-  
methyl-1H-indol-3-yl]methanone; and,
- [1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-  
pyrazol-5-yl][6-[2-[(dimethylamino)methyl]phenyl]-3-  
benzofuranyl]methanone;

or a pharmaceutically acceptable salt form thereof.

45 [8] In another embodiment, the present invention provides  
novel pharmaceutical compositions, comprising: a  
pharmaceutically acceptable carrier and a therapeutically  
effective amount of a compound of the present invention or a  
pharmaceutically acceptable salt form thereof.

50 [9] In another embodiment, the present invention provides a  
novel method for treating or preventing a thromboembolic  
disorder, comprising: administering to a patient in need

5 thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

10 [10] In another embodiment, the present invention provides novel bicyclic compounds as described above for use in therapy.

15 [11] In another embodiment, the present invention provides the use of novel bicyclic compounds as described above for the manufacture of a medicament for the treatment of a thromboembolic disorder.

20 DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to  
25 prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are  
30 contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a  
35 structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention.

40 The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced

5 with a selection from the indicated group, provided that the  
designated atom's normal valency is not exceeded, and that  
the substitution results in a stable compound. When a  
substituent is keto (i.e., =O), then 2 hydrogens on the atom  
are replaced. Keto substituents are not present on aromatic  
10 moieties.

The present invention is intended to include all  
isotopes of atoms occurring in the present compounds.  
Isotopes include those atoms having the same atomic number  
but different mass numbers. By way of general example and  
15 without limitation, isotopes of hydrogen include tritium and  
deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g.,  $R^6$ ) occurs more than one time  
in any constituent or formula for a compound, its definition  
at each occurrence is independent of its definition at every  
20 other occurrence. Thus, for example, if a group is shown to  
be substituted with 0-2  $R^6$ , then said group may optionally  
be substituted with up to two  $R^6$  groups and  $R^6$  at each  
occurrence is selected independently from the definition of  
 $R^6$ . Also, combinations of substituents and/or variables are  
25 permissible only if such combinations result in stable  
compounds.

When a bond to a substituent is shown to cross a bond  
connecting two atoms in a ring, then such substituent may be  
bonded to any atom on the ring. When a substituent is  
30 listed without indicating the atom via which such  
substituent is bonded to the rest of the compound of a given  
formula, then such substituent may be bonded via any atom in  
such substituent. Combinations of substituents and/or  
variables are permissible only if such combinations result  
35 in stable compounds.

As used herein, "alkyl" is intended to include both  
branched and straight-chain saturated aliphatic hydrocarbon  
groups having the specified number of carbon atoms.  $C_{1-6}$   
alkyl, is intended to include  $C_1$ ,  $C_2$ ,  $C_3$ ,  $C_4$ ,  $C_5$ , and  $C_6$   
40 alkyl groups. Examples of alkyl include, but are not  
limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl,



- 5 s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example  $-C_vF_w$  where  $v = 1$  to  $3$  and  $w = 1$  to  $(2v+1)$ ).
- 10 Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge.  $C_{1-6}$  alkoxy, is intended to include  $C_1$ ,  $C_2$ ,  $C_3$ ,  $C_4$ ,  $C_5$ , and  $C_6$  alkoxy groups.
- 15 Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl.  $C_{3-7}$  cycloalkyl, is intended to include  $C_3$ ,  $C_4$ ,  $C_5$ ,  $C_6$ , and  $C_7$  cycloalkyl groups. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any
- 20 stable point along the chain, such as ethenyl and propenyl.  $C_{2-10}$  alkenyl, is intended to include  $C_2$ ,  $C_3$ ,  $C_4$ ,  $C_5$ , and  $C_6$  alkenyl groups. "Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds
- 25 which may occur in any stable point along the chain, such as ethynyl and propynyl.  $C_{2-6}$  alkynyl, is intended to include  $C_2$ ,  $C_3$ ,  $C_4$ ,  $C_5$ , and  $C_6$  alkynyl groups.
- 30

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

35

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or

40 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of

5 such carbocycles include, but are not limited to,  
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,  
cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane,  
[4.3.0]bicyclononane, [4.4.0]bicyclodecane,  
[2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl,  
10 adamantyl, and tetrahydronaphthyl.

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated  
15 or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, NH, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen  
20 and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting  
25 compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the  
30 heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4  
35 heterotams independently selected from the group consisting of N, NH, O and S. It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl,  
40 benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl,

5    benzisoxazolyl, benzisothiazolyl, benzimidazolyl,  
     carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl,  
     chromenyl, cinnolyl, decahydroquinolyl, 2H,6H-1,5,2-  
     dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl,  
     furazanyl, imidazolidinyl, imidazolyl, imidazolyl, 1H-  
10    indazolyl, indolenyl, indolyl, indolizyl, indolyl, 3H-  
     indolyl, isobenzofuranyl, isochromanyl, isoindazolyl,  
     isoindolyl, isoindolyl, isoquinolyl, isothiazolyl,  
     isoxazolyl, methylenedioxyphenyl, morpholyl,  
     naphthyridinyl, octahydroisoquinolyl, oxadiazolyl, 1,2,3-  
15    oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-  
     oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl,  
     pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl,  
     phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl,  
     piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl,  
20    piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl,  
     pyrazolidinyl, pyrazolyl, pyrazolyl, pyridazinyl,  
     pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl,  
     pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl,  
     pyrrolyl, quinazolyl, quinolyl, 4H-quinolizyl,  
25    quinoxalyl, quinuclidinyl, tetrahydrofuranyl,  
     tetrahydroisoquinolyl, tetrahydroquinolyl, tetrazolyl,  
     6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-  
     thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl,  
     thianthrenyl, thiazolyl, thienyl, thienothiazolyl,  
30    thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl,  
     1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-  
     triazolyl, and xanthenyl. Also included are fused ring and  
     spiro compounds containing, for example, the above  
     heterocycles.

35        The phrase "pharmaceutically acceptable" is employed  
     herein to refer to those compounds, materials, compositions,  
     and/or dosage forms which are, within the scope of sound  
     medical judgment, suitable for use in contact with the  
     tissues of human beings and animals without excessive  
40    toxicity, irritation, allergic response, or other problem or

5 complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts  
10 thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the  
15 conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric,  
20 sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-  
25 acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical  
30 methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate,  
35 ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

40 Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility,

5 bioavailability, manufacturing, etc...) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are  
10 intended to include any covalently bonded carriers which release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the present invention are prepared by modifying functional groups present in the compound in such  
15 a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is  
20 administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the  
25 present invention. Preferred prodrugs are amidine prodrugs wherein D is  $C(=NR^7)NH_2$  or its tautomer  $C(=NH)NHR^7$  and  $R^7$  is selected from OH,  $C_{1-4}$  alkoxy,  $C_{6-10}$  aryloxy,  $C_{1-4}$  alkoxycarbonyl,  $C_{6-10}$  aryloxycarbonyl,  $C_{6-10}$  arylmethylcarbonyl,  $C_{1-4}$  alkylcarbonyloxy,  $C_{1-4}$  alkoxycarbonyl, and  $C_{6-10}$  arylcarbonyloxy,  $C_{1-4}$  alkoxycarbonyl. More preferred prodrugs are where  $R^7$  is OH, methoxy, ethoxy, benzyloxycarbonyl, methoxycarbonyl, and methylcarbonyloxymethoxycarbonyl.

"Stable compound" and "stable structure" are meant to  
35 indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Substituted" is intended to indicate that one or more  
40 hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the

5 indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

"Therapeutically effective amount" is intended to  
10 include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective to inhibit factor Xa. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, *Adv. Enzyme Regul.* 1984,  
15 22, 27-55, occurs when the effect (in this case, inhibition of factor Xa) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated  
20 at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

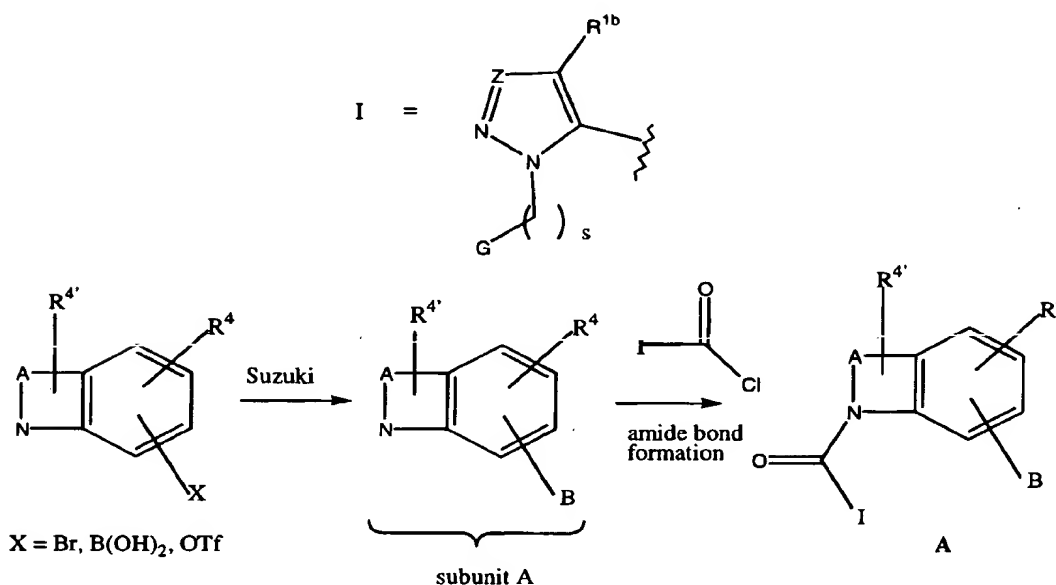
25

## SYNTHESIS

The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below,  
30 together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the  
35 reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes  
40 require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the

invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, 1991). All references cited herein are hereby incorporated in their entirety herein by reference.

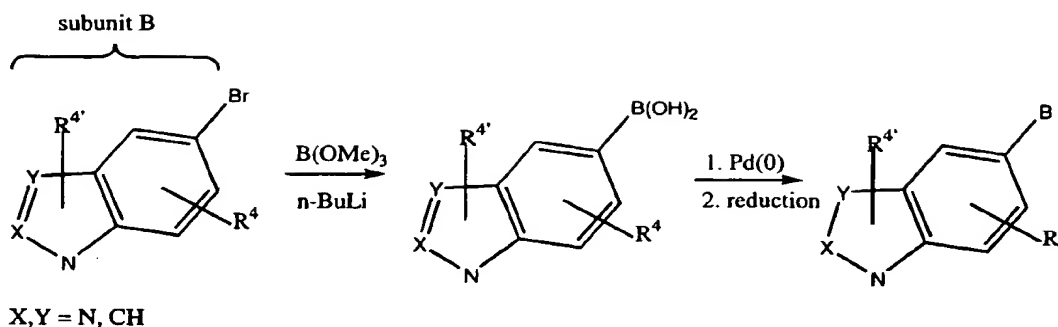
Scheme 1



A general procedure for making compounds of type A is described in Scheme 1. A preferred method for making an amide bond is treatment of the acid chloride of compounds of formula I with the sodium or potassium salt of subunit A in a solvent such as tetrahydrofuran or methylene chloride, followed by further manipulations as outlined in W097/23212, W098/28282, W098/28269, W098/57937, W098/57951, and PCT/US98/26427, the contents of which are incorporated herein by reference, should lead to compounds of the present invention..

5

Scheme 2

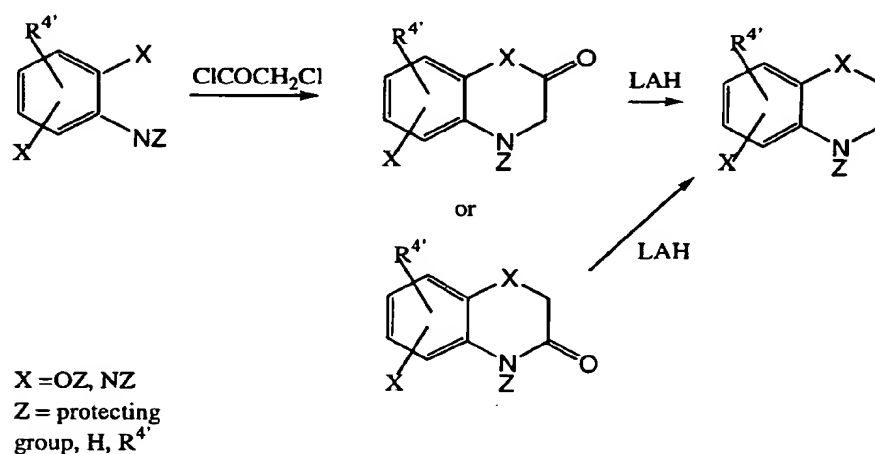


Preparation of subunit **B** can be done by means of the Suzuki reaction and is shown generically in Scheme 2. The generation of boronic acid from the corresponding bromide proceeds via halogen-metal exchange of the bromine with n-BuLi, followed by the quenching of the reaction mixture with triisopropylborate and acidic hydrolysis. The Suzuki reaction proceeds according to standard protocols, followed, when necessary, by reduction of the heterocyclic ring double bond. The subunit **B** can be already linked to the rest of the molecule, before the Suzuki reaction.

General and specific Schemes describing synthesis of subunit **B** of this invention are outlined in Schemes 3-12.

20

Scheme 3

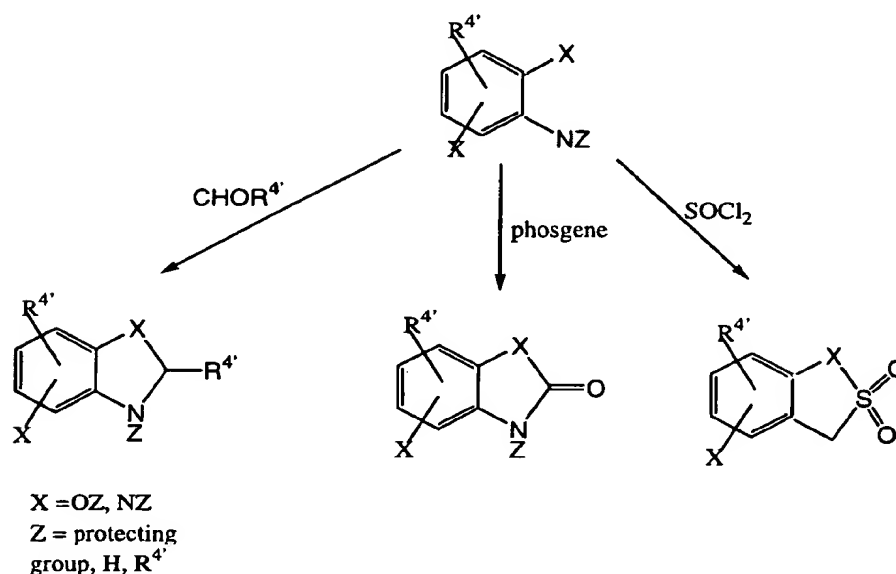


Preparation of the compounds in this Scheme commences by the treatment of the appropriately substituted aniline



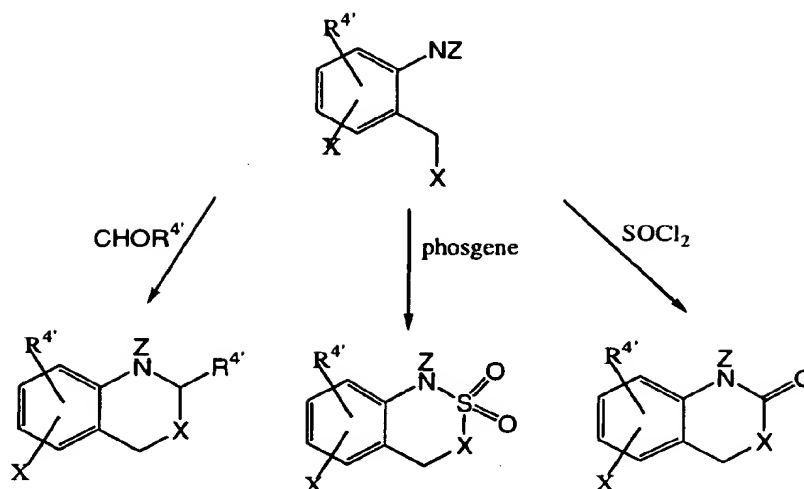
- 5 with chloroacetyl chloride in the presence of the mild base in chloroform (see Huang et. al., *Synthesis* **1984**, 851). The regioselectivity of the addition is dependent upon the choice of protecting groups. Reduction with LAH of either regioisomer produces the desired products.

10

**Scheme 3a**

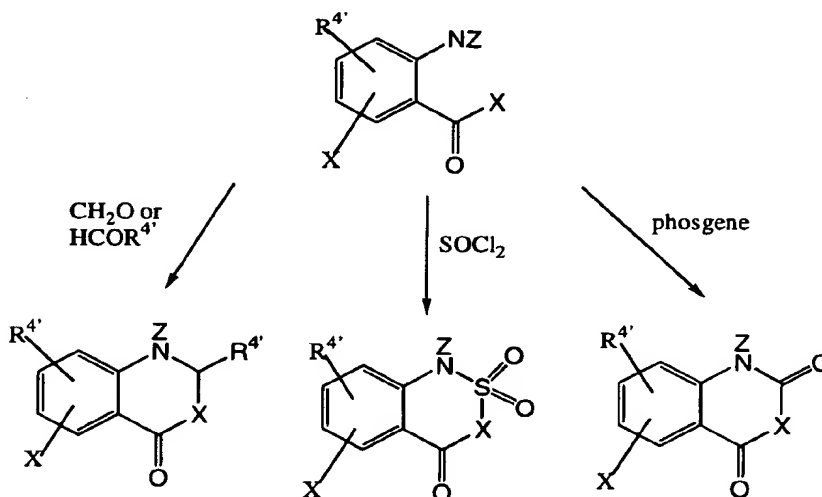
- 15 Synthesis of various fused 5-ring heterocycles can be accomplished as outlined in Scheme 3a. An appropriately substituted aniline can be reacted with the appropriate reagents outlined in the scheme according to the methods known to those in the art to give the desired products.

5

**Scheme 4**

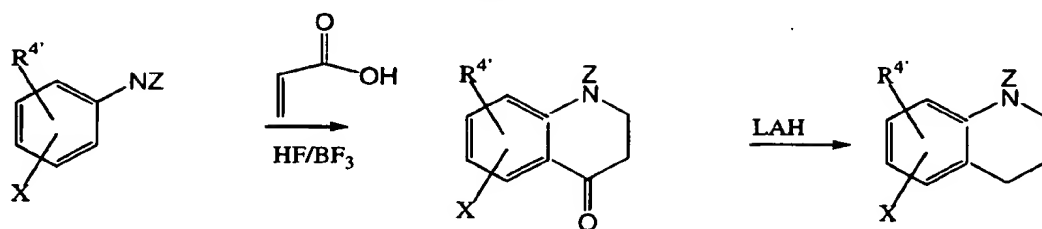
Synthesis of various 6-ring fused heterocycles shown in Scheme 4 follows the protocols outlined in Scheme 3a.

10

**Scheme 5**

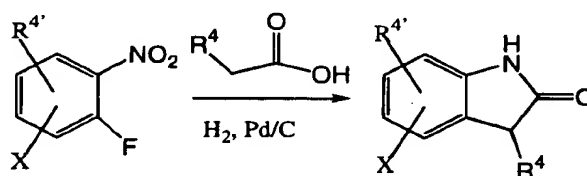
Synthesis of 6-ring fused heterocycles shown in Scheme 5 are similar to the methods described in Scheme 3a.

5

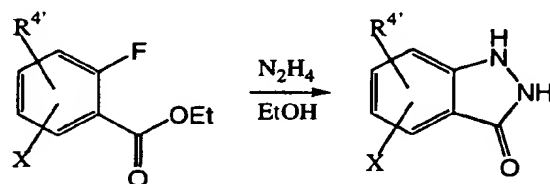
**Scheme 6**

Synthesis of compounds described in Scheme 6 can be accomplished by reacting an appropriately substituted aniline with the acrylic acid, followed by Friedel-Crafts reaction in the presence of HF and BF<sub>3</sub> under pressure according to the protocol in WO94/412,075, followed by the reduction with LAH to afford the desired compounds.

15

**Scheme 7**

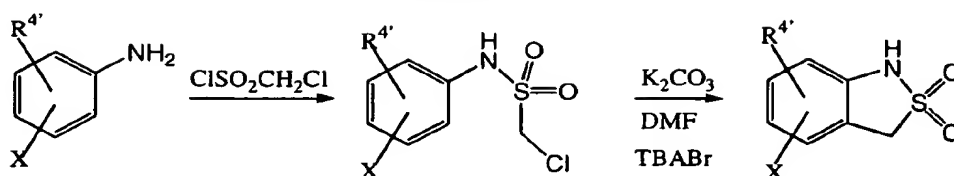
In Scheme 7, an appropriately substituted p-nitro-fluorobenzene can be reduced with hydrogen over Pd/C in the presence of derivatized acetic acid to effect closure to a desired benzolactam.

**Scheme 8**

25

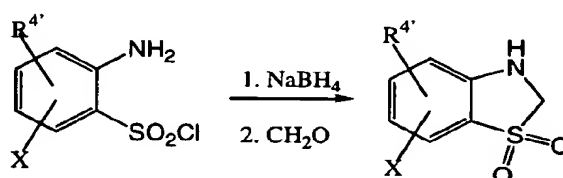
In Scheme 8, an appropriately substituted p-carboethoxy-fluorobenzene can react with hydrazine in ethanol to effect cyclization to a desired benzoazalactam.

5

**Scheme 9**

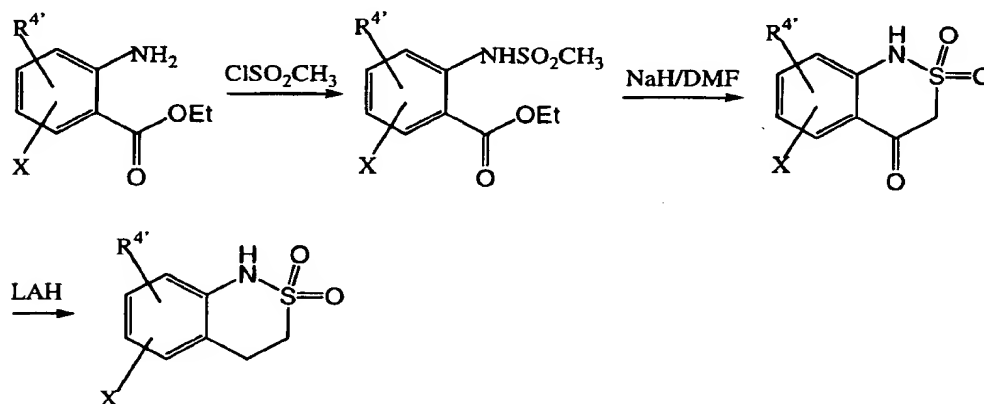
Synthesis of compounds shown in Scheme 9 can be accomplished according to the procedure by Wojciechowski et. al., *Synthesis* **1992**, 6, 571. Treatment of an appropriately substituted aniline with chloromethylsulfonyl chloride can be followed by the closure to the sulfonamide ring under basic conditions in DMF in the presence of *tert*-butyl ammonia bromide to afford the desired compounds.

15

**Scheme 10**

Preparation of compounds in Scheme 10 can proceed via reductive amination of the substituted o-amino-benzosulfonyl chloride in the presence of formaldehyde to afford the desired compound.

20

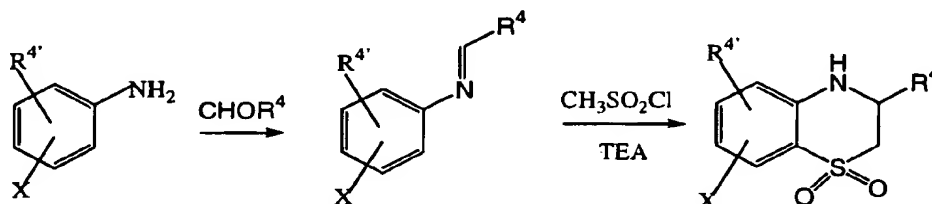
**Scheme 11**

25

5

Compounds in Scheme 11 can be obtained following the protocol by Lombardino et al., *J. Heterocycl. Chem* **1979**, 9. Treatment of the intermediate sulfonamide, obtained by conventional methods, with sodium hydride in DMF effects ring closure. Subsequent reduction with LAH produces the desired compound.

Scheme 12



15

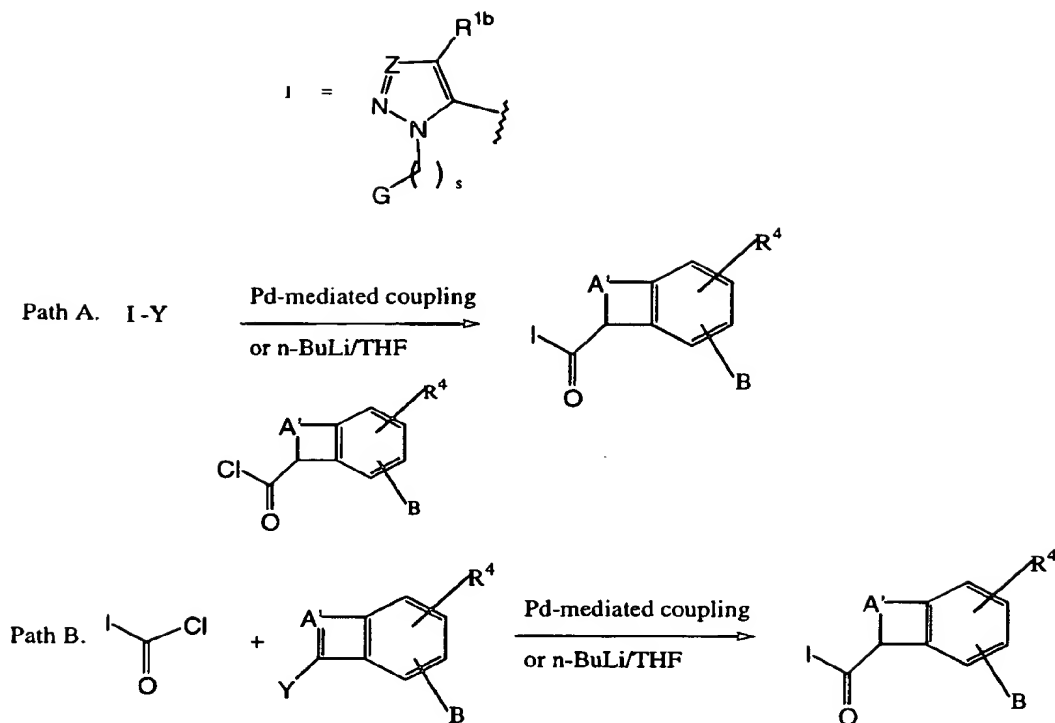
Compounds in Scheme 12 can be obtained by the methodology of Rai et. al. (*Chem. Ind., London* **1979**, 26) by treatment of an intermediate substituted imine, obtained by the conventional methods, with methanesulfonyl chloride in THF.

20

5

## Scheme 13

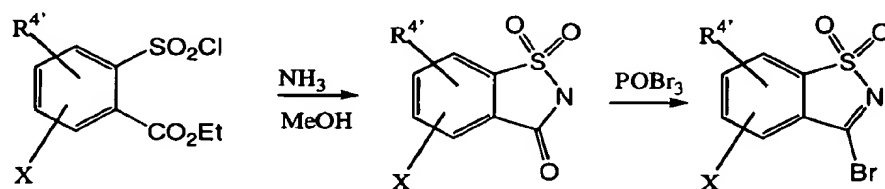
For structure B

Y = Br, I, ZnCl, Sn(Bu)<sub>3</sub>

General procedures for making the carbon-linked compounds of type B are presented in Scheme 13. Cross coupling reactions of this type are well known to those of skill in the art (see Negishi, *Tetr. Lett.* **1980**, 24, 5181 or Sakamoto et. al., *Heterocycles* **1992**, 2, 813 for palladium mediated coupling and Baxter et. al., *J. Med. Chem.* **1993**, 36, 2739 or Pavlik et. al., *J. Heterocycl. Chem.* **1992**, 1357 for n-BuLi reactions). Path A or B can be selected dependent on the ease of the synthesis of the right hand subunit. After the coupling reaction is complete the further manipulations, to obtain the final compounds of interest, are done according to WO97/23212, WO98/28282, WO98/28269, WO98/57937, WO98/57951, and PCT/US98/26427, the contents of which are incorporated herein by reference.

- 5 General preparations of the intermediates for the cross coupling reactions are outlined in the following Schemes.

Scheme 14

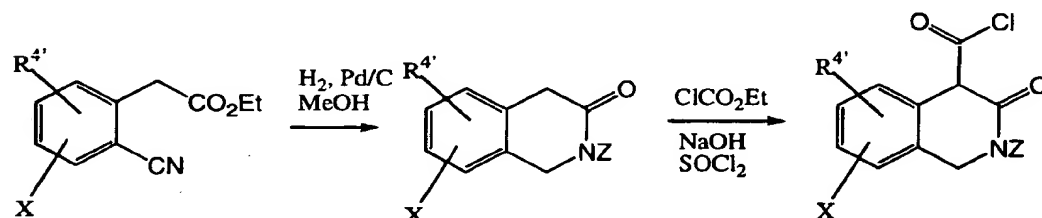


10

Intermediates useful for making compounds of the present invention can be prepared as shown in Scheme 14. An appropriately substituted phenylsulfonyl chloride can be treated with ammonia in methanol to afford an intermediate, which can be converted to the bromo-derivative after reacting with  $\text{POBr}_3$ . This compound undergoes a cross coupling reaction as outlined in Scheme 13, Path B.

15

Scheme 15



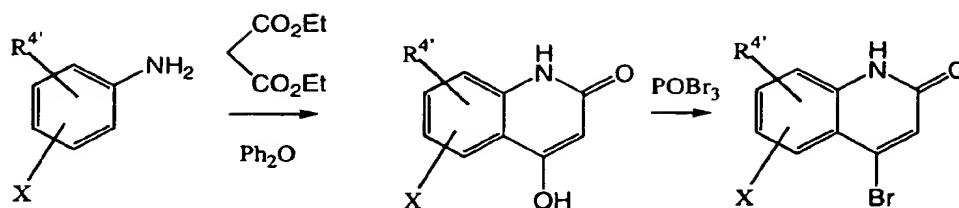
20

The compounds described in Scheme 15 can be prepared by reduction and subsequent cyclization of an appropriately substituted benzonitrile, followed by treatment with ethyl chloroformate in the presence of a strong base such as LDA. The intermediate ester can be hydrolyzed to the acid with NaOH in THF and water and converted to the acid chloride upon refluxing with thionyl chloride in a solvent such as methylene chloride or tetrahydrofuran. The target compounds then can be obtained via Path A, Scheme 13.

25

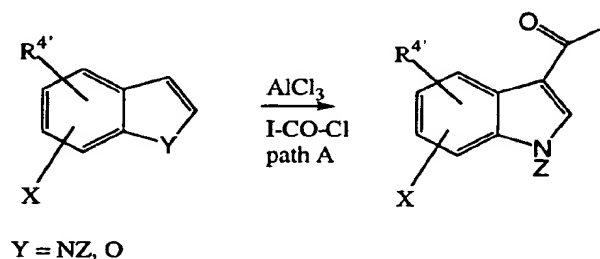
30

5

**Scheme 16**

The compounds described in Scheme 16 can be obtained by the methodology of Yamaguchi et. al., *J. Heterocycl. Chem.* **1990**, 27, 999. An appropriately substituted aniline can be reacted with diethylmalonate in diphenyl ether, followed by the treatment with POBr<sub>3</sub> to afford the bromide. The desired compounds then can be prepared according to Path B, Scheme 13.

15

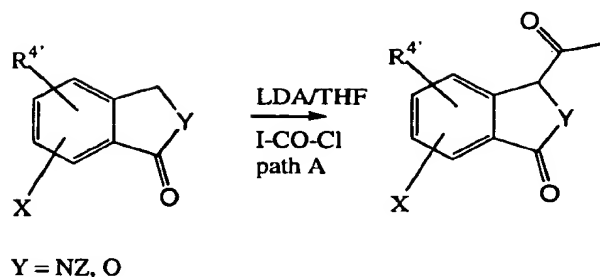
**Scheme 17**

The compounds of this invention can be obtained by the Friedel-Crafts reaction between an appropriately substituted indole or benzofuran and an acid chloride of the compounds of formula I in the presence of AlCl<sub>3</sub>, as described by Murakami et. al., *Chem. Pharm. Bull.* **1988**, 36, 2023 and Kwiecien et. al., *J. Heterocycl. Chem.* **1997**, 34, 1587.

25

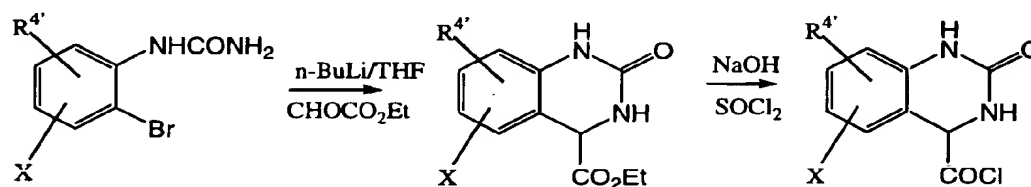


5

**Scheme 18**

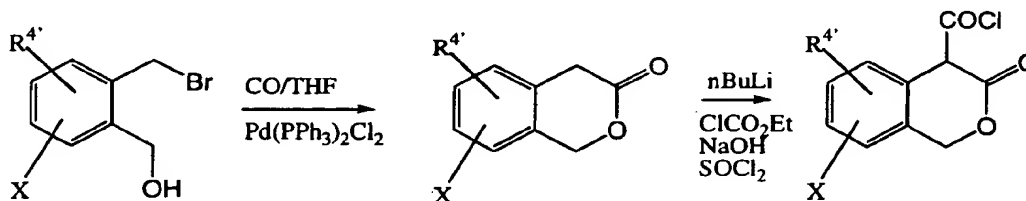
As shown in Scheme 18, treatment of an appropriately substituted benzolactam or lactone, obtained by the methods known to those of skill in the art, with a strong base such as LDA, followed by addition of an acid chloride of formula I can afford the desired compounds.

15

**Scheme 19**

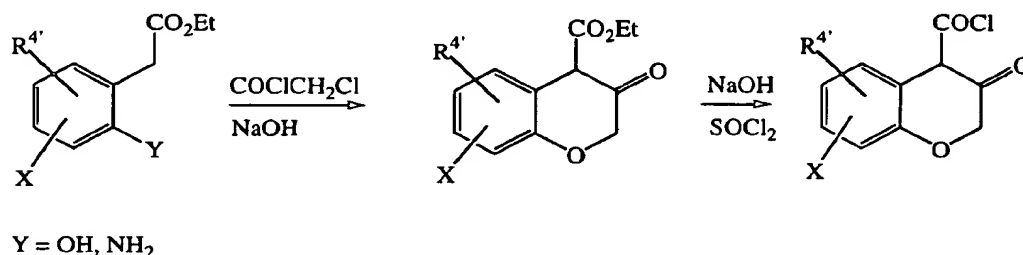
Preparation of compounds of Scheme 19 can proceed via halogen-metal exchange of a substituted benzourea and quenching the anion with ethyl glyoxylate to produce the cyclization product. Conversion of the ester to the acid chloride under standard conditions (Scheme 15) and further manipulation via path A, Scheme 13 leads to the desired products.

25

**Scheme 20**

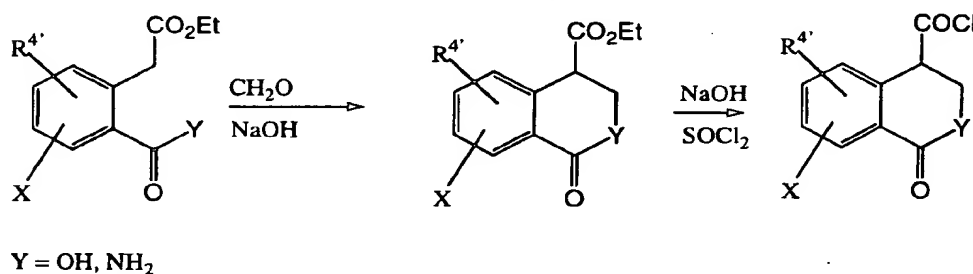
5 As shown in Scheme 20, intermediate benzolactones can be prepared from readily available starting materials upon treatment with carbon monoxide in THF in the presence of a catalytic amount of Pd(0). Further elaboration to the corresponding acid chloride follows the procedure outlined in Scheme 15.

Scheme 21



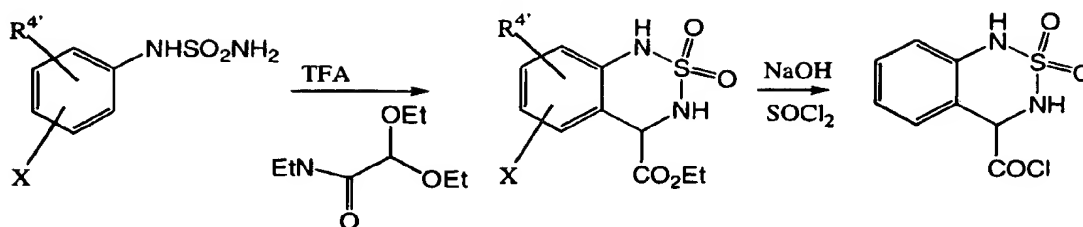
15 Synthesis of the compounds shown in Scheme 21 can be accomplished according to the protocols described in Schemes 3 and 15.

Scheme 22



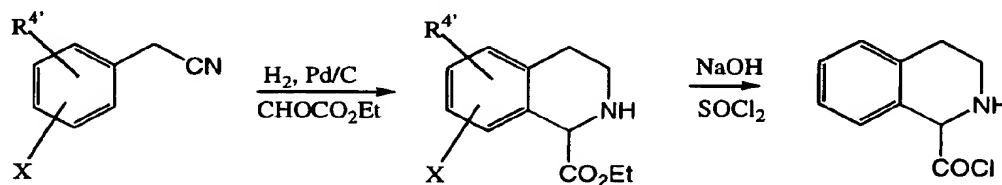
20 In the case of compounds shown in Scheme 22, the desired benzolactams and lactones can be generated from available starting materials in a basic media with formaldehyde and an appropriate solvent. Conversion to the corresponding acid chloride can be achieved as described in Scheme 15.

5

**Scheme 23**

Preparation of the cyclic benzosulfonyl ureas shown in Scheme 23 can follow methodology described by Lee et. al.,  
 10 *J. Org. Chem.* **1990**, *25*, 6098. Generation of the acid chloride from the corresponding ester can be similar to the procedure of Scheme 15.

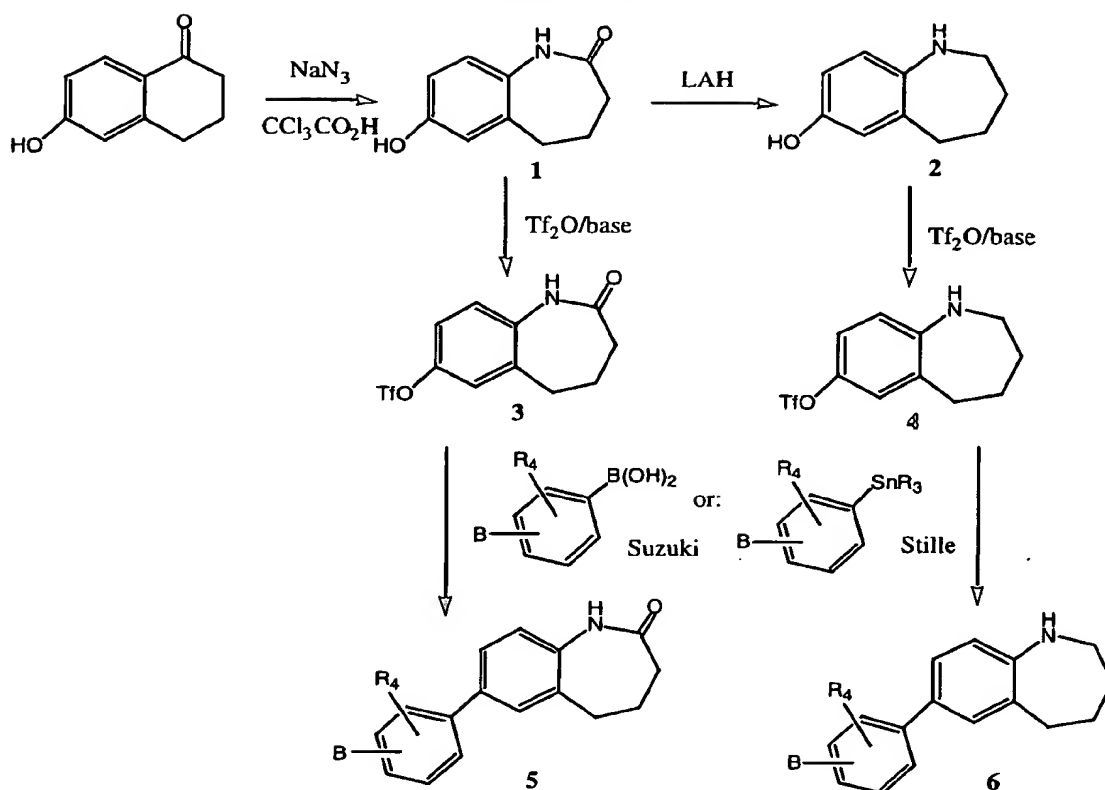
15

**Scheme 24**

Preparation of compounds outlined in Scheme 24 can proceed from readily available benzylic nitriles. Reduction with hydrogen over  $Pd/C$  and subsequent ring closure upon  
 20 treatment with ethyl glyoxylate can provide an intermediate ester, that can be converted to an acid chloride following Scheme 15.

5

Scheme 25

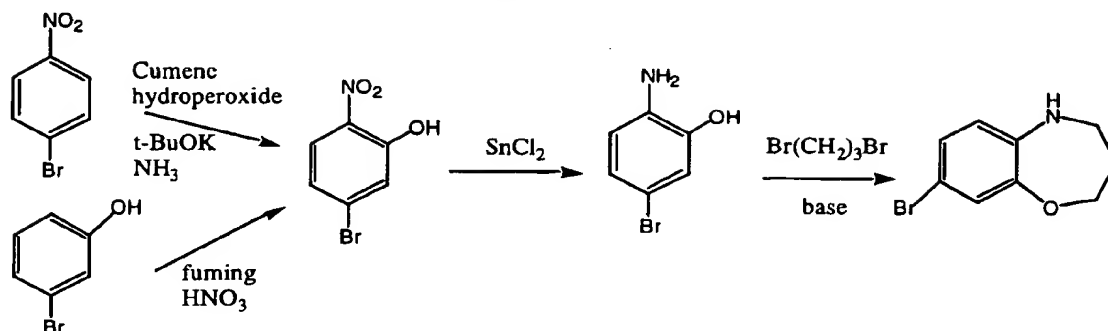


Compounds of formula **A** where **A** is  $-(\text{CH}_2)_2-$  and  $-\text{CO}(\text{CH}_2)_3-$  can be prepared by Schmidt rearrangement of 6-hydroxy-tetralone (Scheme 1). Treatment of 6-hydroxy-tetralone with sodium azide-trichloroacetic acid can afford hydroxybenzazepine 1, which can be reduced by  $\text{LiAlH}_4$  to benzazepine 2 (see Valderrama et al. *Syn. Comm.* **1992**, 22(4), 629-639). The hydroxy group of 1 and 2 can be then converted to triflate 3 and 4, which can undergo cross coupling with organoboron or organotin compounds (see a review by Ritter, *Synthesis*, "Synthetic Transformations of vinyl and aryl Triflates", **1993**, 735-762) to give compounds 5 and 6.

Compounds of formula **A** where **A** is  $-(\text{CH}=\text{CH})_2-$ ,  $-\text{CH}_2\text{CH}=\text{CHCH}_2-$ ,  $-\text{CH}=\text{CH}(\text{CH}_2)_2-$ , and  $-(\text{CH}_2)_2\text{CH}=\text{CH}-$  can be prepared by literature methods (see *Tetr. Lett.* **1985**, 26(24), 2827-2830; *Bull. Soc. Chim. Fr.* **1992**, 130(2), 143-145; *Tetr.*

- 5 *Lett.* **1985**, 26(5), 685-688 *Synthesis* **1985**, 6-7, 612-619; and *Aust. J. Chem.* **1986**, 39(3), 529-539).

Scheme 26

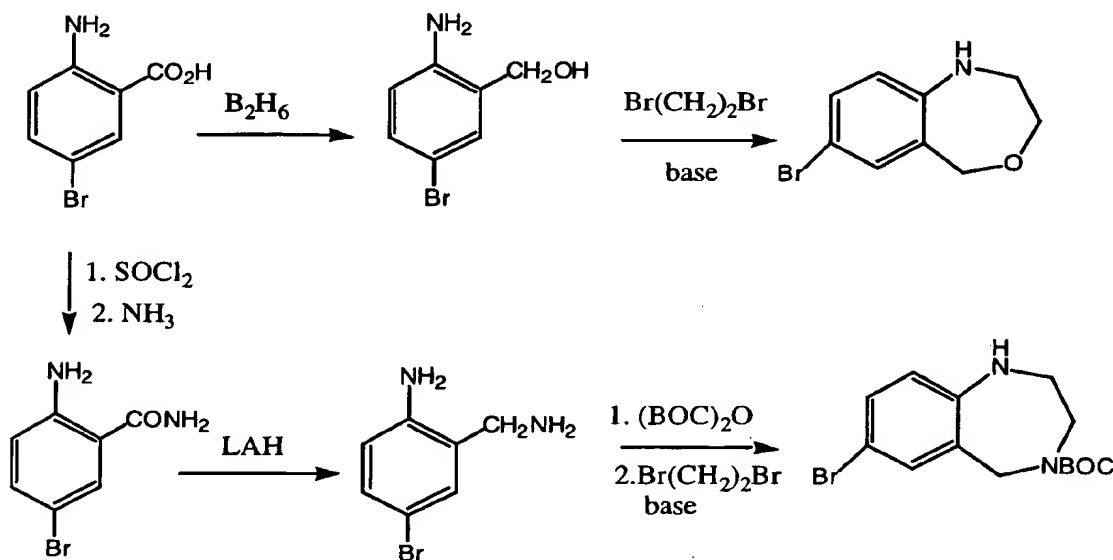


10

Compounds of formula **A** where **A** is -(CH<sub>2</sub>)<sub>3</sub>O- can be prepared as shown in Scheme 26 from 2-amino-5-bromophenol, which can be prepared from the methods either by Makosza (*J. Org. Chem.* **1998**, 63(13), 4199-4208) or Hanzlik (*J. Org. Chem.* **1990**, 55(9), 2763-2742).

15

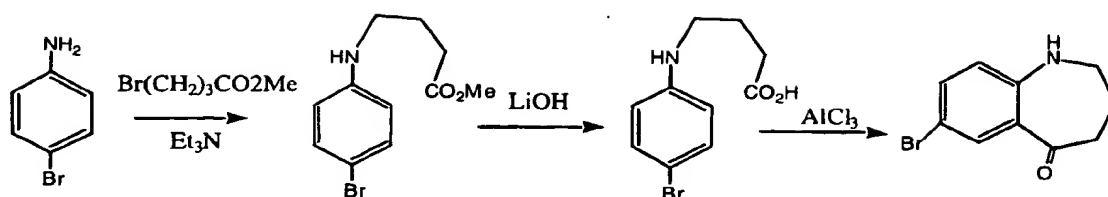
Scheme 27



20

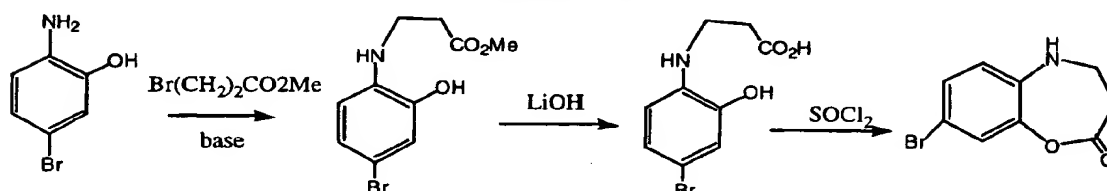
Compounds of formula **A** where **A** is -(CH<sub>2</sub>)<sub>2</sub>OCH<sub>2</sub>- and -(CH<sub>2</sub>)<sub>2</sub>NCH<sub>2</sub>- can be prepared from 2-amino-5-bromobenzoic acid as shown in Scheme 27.

5

**Scheme 28**

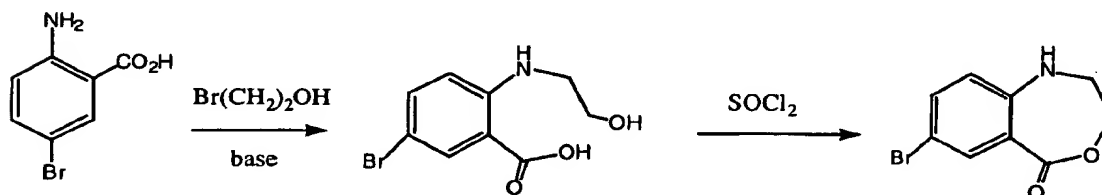
Compounds of formula **A** where **A** is  $-(\text{CH}_2)_3\text{CO}-$  can be prepared from 4-bromoaniline as shown in Scheme 28.

10

**Scheme 29**

Compounds of formula **A** where **A** is  $-(\text{CH}_2)_2\text{CO}-$  can be prepared from 4-bromoaniline as shown in Scheme 29.

15

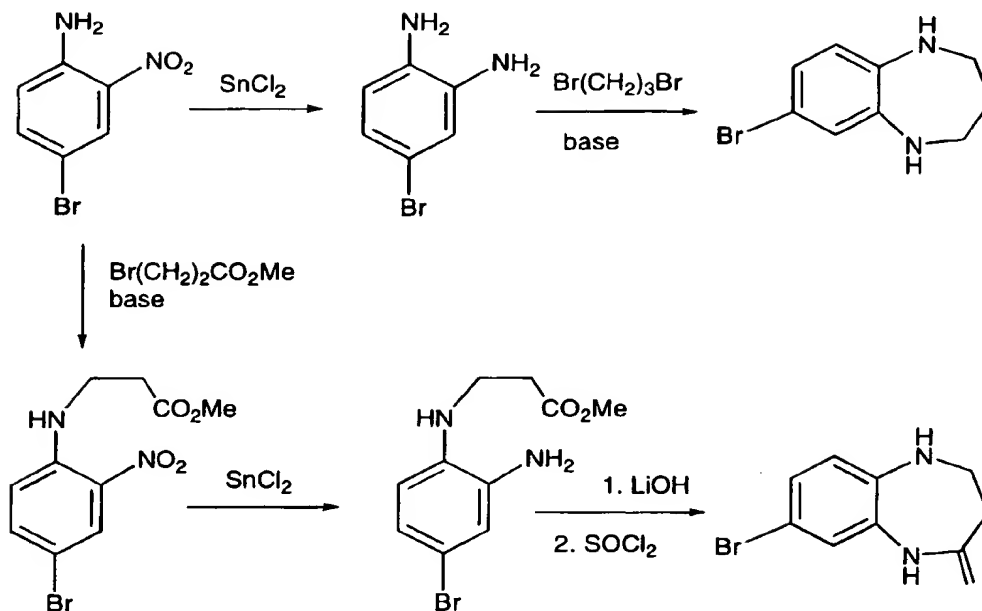
**Scheme 30**

20

Compounds of formula **A** where **A** is  $-(\text{CH}_2)_2\text{OCO}-$  can be prepared from 4-bromoaniline as shown in Scheme 30.

5

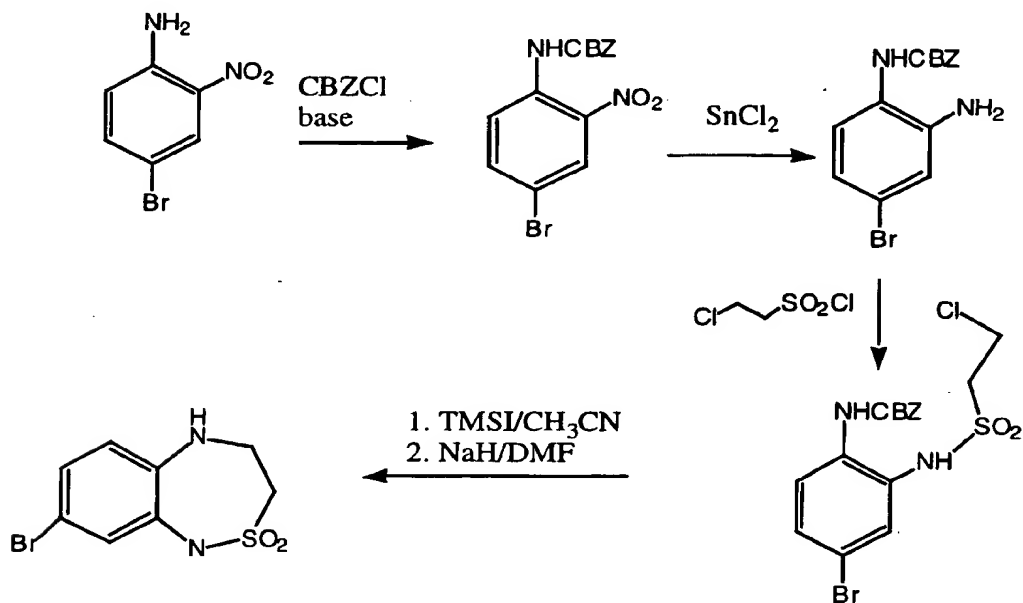
Scheme 31



Compounds of formula **A** where **A** is  $-(\text{CH}_2)_3\text{N}-$  and  $-(\text{CH}_2)_2\text{CON}-$  can be prepared from 4-bromo-2-nitroaniline as shown in Scheme 31.

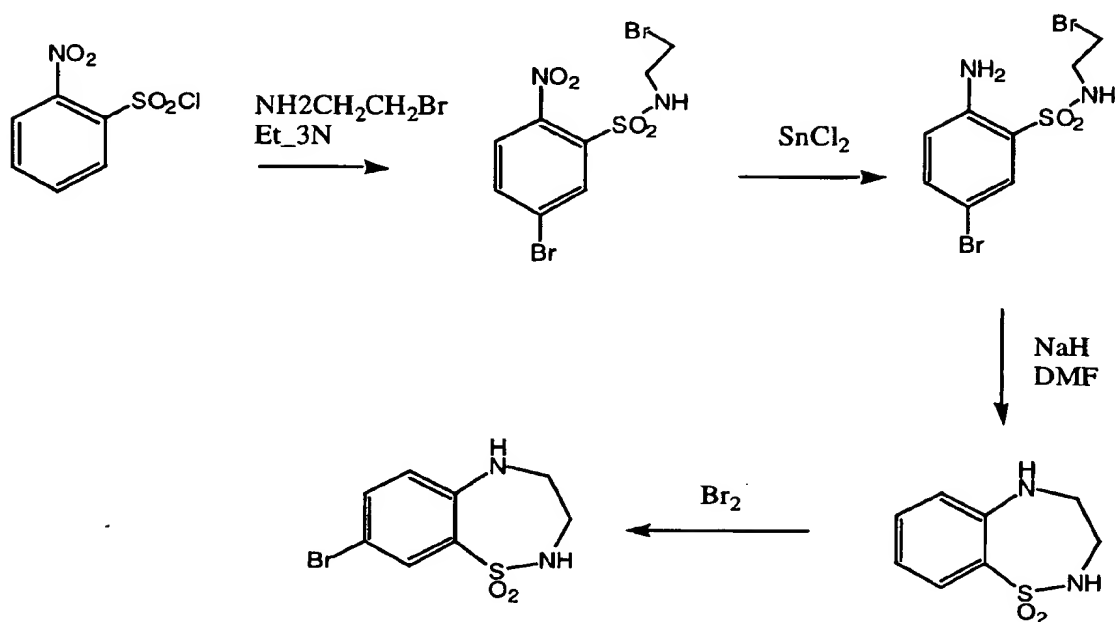
10

Scheme 32



- 5 Compounds of formula **A** where **A** is  $-(CH_2)_2SO_2N-$  and  $-(CH_2)_2NSO_2-$  can be prepared as shown in Scheme 32 and 33 respectively.

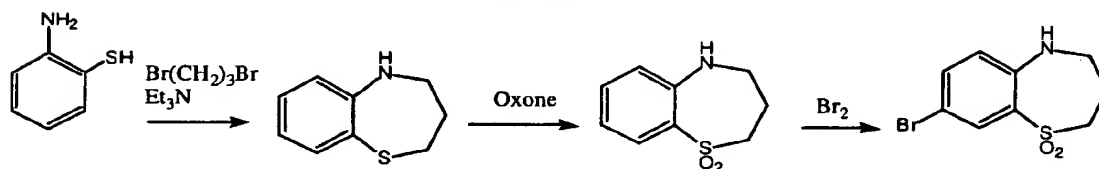
Scheme 33



- Compounds of formula **A** where **A** is  $-(CH_2)_2SO_2-$  and  $-(CH_2)_2SO_2CH_2-$  can be prepared as shown in Scheme 34 and 35.

15

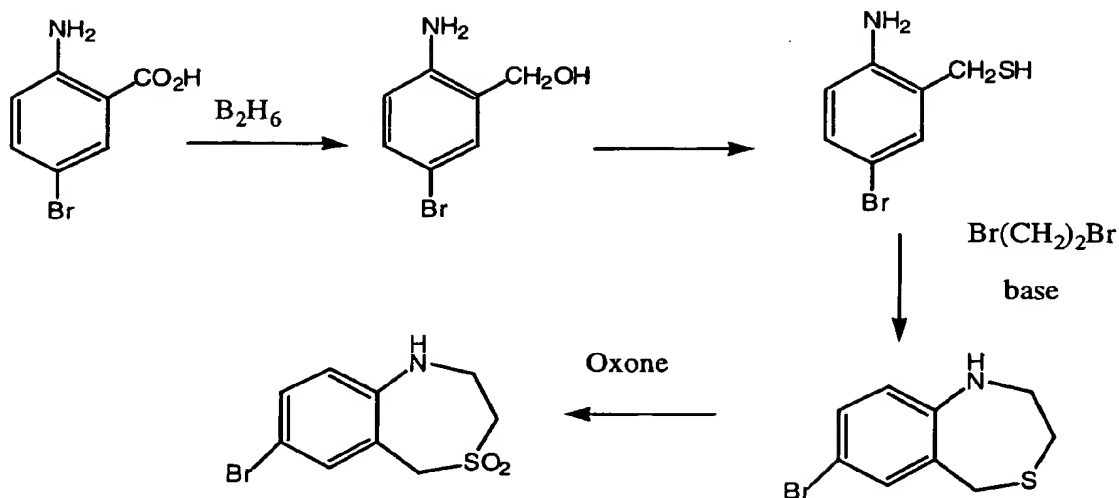
Scheme 34



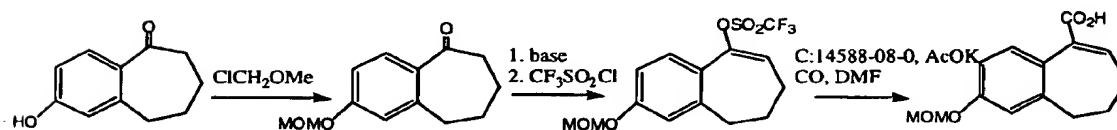


5

Scheme 35



Scheme 36

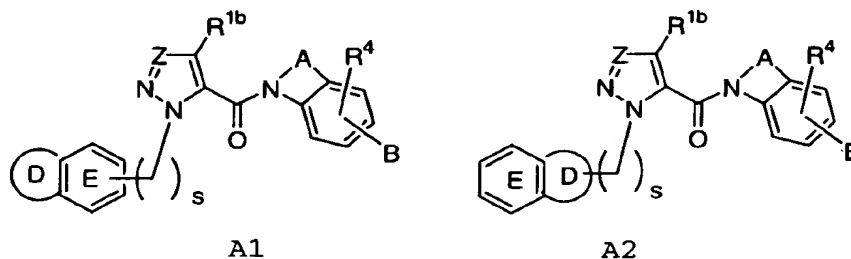


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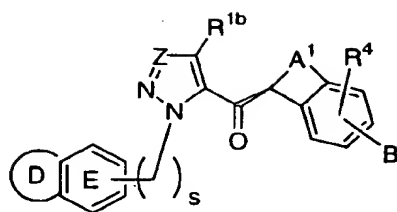
Compounds of formula **B** where  $A^1$  is  $-CH=CH(CH_2)_3-$  can be prepared as shown in Scheme 36. The hydroxy group of benzosuberone (see *India. Org. Prep. Proced. Int.* **1992**, 24(1), 27-32) can be protected with the MOM group and then the ketone group can be converted to enol trifluoromethylsulfonate, which can then be converted to the carboxylic acid (see *Tetra. Lett.* **1992**, 33(27), 3939-3942).

15

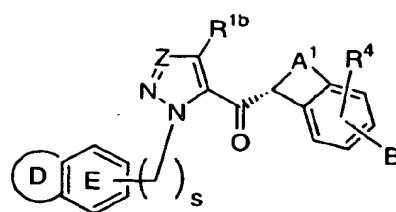
Preferred compounds of the present invention are compounds of formulas A1-A2 and B1-B4 show below:



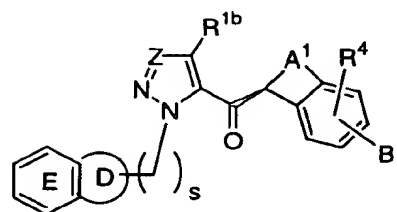
20



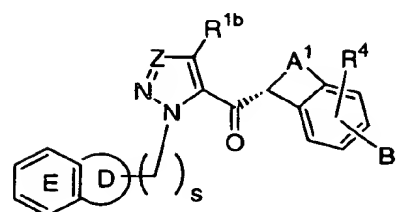
B1



B2



B3



B4

or pharmaceutically acceptable salt forms thereof.

#### UTILITY

The compounds of this invention are useful as  
 15 anticoagulants for the treatment or prevention of  
 thromboembolic disorders in mammals. The term  
 "thromboembolic disorders" as used herein includes arterial  
 or venous cardiovascular or cerebrovascular thromboembolic  
 disorders, including, for example, unstable angina, first or  
 20 recurrent myocardial infarction, ischemic sudden death,  
 transient ischemic attack, stroke, atherosclerosis, venous  
 thrombosis, deep vein thrombosis, thrombophlebitis, arterial  
 embolism, coronary and cerebral arterial thrombosis,  
 cerebral embolism, kidney embolisms, and pulmonary  
 25 embolisms. The anticoagulant effect of compounds of the  
 present invention is believed to be due to inhibition of  
 factor Xa or thrombin.

The effectiveness of compounds of the present invention  
 as inhibitors of factor Xa was determined using purified  
 30 human factor Xa and synthetic substrate. The rate of factor  
 Xa hydrolysis of chromogenic substrate S2222 (Kabi  
 Pharmacia, Franklin, OH) was measured both in the absence  
 and presence of compounds of the present invention.

5 Hydrolysis of the substrate resulted in the release of pNA, which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nm. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay  
10 are expressed as inhibitory constant,  $K_i$ .

Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5 % PEG 8000. The Michaelis constant,  $K_m$ , for substrate hydrolysis was determined at 25°C using the method of  
15 Lineweaver and Burk. Values of  $K_i$  were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate (0.20 mM-1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 minutes and the velocities (rate of  
20 absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship was used to calculate  $K_i$  values:

$$(v_o - v_s) / v_s = I / (K_i (1 + S / K_m))$$

where:

25  $v_o$  is the velocity of the control in the absence of inhibitor;  
 $v_s$  is the velocity in the presence of inhibitor;  
 $I$  is the concentration of inhibitor;  
 $K_i$  is the dissociation constant of the enzyme:inhibitor  
30 complex;  
 $S$  is the concentration of substrate;  
 $K_m$  is the Michaelis constant.

Using the methodology described above, a number of compounds of the present invention were found to exhibit a  $K_i$  of  $\leq 10$   
35  $\mu\text{M}$ , thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

Compounds tested in the above assay are considered to be active if they exhibit a  $K_i$  of  $\leq 10$   $\mu\text{M}$ . Preferred compounds of the present invention have  $K_i$ 's of  $\leq 1$   $\mu\text{M}$ . More  
40 preferred compounds of the present invention have  $K_i$ 's of  $\leq 0.1$   $\mu\text{M}$ . Even more preferred compounds of the present

5 invention have  $K_i$ 's of  $\leq 0.01 \mu\text{M}$ . Still more preferred compounds of the present invention have  $K_i$ 's of  $\leq 0.001 \mu\text{M}$ .

The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model. In this model, rabbits  
10 weighing 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing which  
15 contains a piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread will induce the formation of a significant thrombus. After forty minutes, the shunt is disconnected and the silk thread covered with  
20 thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group. The ID50 values (dose which produces 50% inhibition of thrombus formation) are  
25 estimated by linear regression.

The compounds of the present invention may also be useful as inhibitors of serine proteases, notably human thrombin, plasma kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for use in  
30 the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes. Specifically, the compounds have utility as drugs for the treatment of diseases arising from elevated thrombin activity such as myocardial  
35 infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin  
40 by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. *In vitro*

5 inhibition constants were determined by the method described  
by Kettner et al. in *J. Biol. Chem.* **265**, 18289-18297 (1990),  
herein incorporated by reference. In these assays,  
thrombin-mediated hydrolysis of the chromogenic substrate  
S2238 (Helena Laboratories, Beaumont, TX) was monitored  
10 spectrophotometrically. Addition of an inhibitor to the  
assay mixture results in decreased absorbance and is  
indicative of thrombin inhibition. Human thrombin (Enzyme  
Research Laboratories, Inc., South Bend, IN) at a  
concentration of 0.2 nM in 0.10 M sodium phosphate buffer,  
15 pH 7.5, 0.20 M NaCl, and 0.5% PEG 6000, was incubated with  
various substrate concentrations ranging from 0.20 to 0.02  
mM. After 25 to 30 minutes of incubation, thrombin activity  
was assayed by monitoring the rate of increase in absorbance  
at 405 nm which arises owing to substrate hydrolysis.  
20 Inhibition constants were derived from reciprocal plots of  
the reaction velocity as a function of substrate  
concentration using the standard method of Lineweaver and  
Burk. Using the methodology described above, some compounds  
of this invention were evaluated and found to exhibit a  $K_i$   
25 of less than 10  $\mu$ M, thereby confirming the utility of the  
compounds of the present invention as effective thrombin  
inhibitors.

The compounds of the present invention can be  
administered alone or in combination with one or more  
30 additional therapeutic agents. These include other anti-  
coagulant or coagulation inhibitory agents, anti-platelet or  
platelet inhibitory agents, thrombin inhibitors, or  
thrombolytic or fibrinolytic agents.

The compounds are administered to a mammal in a  
35 therapeutically effective amount. By "therapeutically  
effective amount" it is meant an amount of a compound of the  
present invention that, when administered alone or in  
combination with an additional therapeutic agent to a  
mammal, is effective to prevent or ameliorate the  
40 thromboembolic disease condition or the progression of the  
disease.

5 By "administered in combination" or "combination  
therapy" it is meant that the compound of the present  
invention and one or more additional therapeutic agents are  
administered concurrently to the mammal being treated. When  
administered in combination each component may be  
10 administered at the same time or sequentially in any order  
at different points in time. Thus, each component may be  
administered separately but sufficiently closely in time so  
as to provide the desired therapeutic effect. Other  
anticoagulant agents (or coagulation inhibitory agents) that  
15 may be used in combination with the compounds of this  
invention include warfarin and heparin, as well as other  
factor Xa inhibitors such as those described in the  
publications identified above under Background of the  
Invention.

20 The term anti-platelet agents (or platelet inhibitory  
agents), as used herein, denotes agents that inhibit  
platelet function such as by inhibiting the aggregation,  
adhesion or granular secretion of platelets. Such agents  
include, but are not limited to, the various known  
25 non-steroidal anti-inflammatory drugs (NSAIDS) such as  
aspirin, ibuprofen, naproxen, sulindac, indomethacin,  
mefenamate, droxicam, diclofenac, sulfinpyrazone, and  
piroxicam, including pharmaceutically acceptable salts or  
prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic  
30 acid or ASA), and piroxicam are preferred. Other suitable  
anti-platelet agents include ticlopidine, including  
pharmaceutically acceptable salts or prodrugs thereof.  
Ticlopidine is also a preferred compound since it is known  
to be gentle on the gastro-intestinal tract in use. Still  
35 other suitable platelet inhibitory agents include IIb/IIIa  
antagonists, thromboxane-A<sub>2</sub>-receptor antagonists and  
thromboxane-A<sub>2</sub>-synthetase inhibitors, as well as  
pharmaceutically acceptable salts or prodrugs thereof.

The term thrombin inhibitors (or anti-thrombin agents),  
40 as used herein, denotes inhibitors of the serine protease  
thrombin. By inhibiting thrombin, various thrombin-mediated

5 processes, such as thrombin-mediated platelet activation  
(that is, for example, the aggregation of platelets, and/or  
the granular secretion of plasminogen activator inhibitor-1  
and/or serotonin) and/or fibrin formation are disrupted. A  
number of thrombin inhibitors are known to one of skill in  
10 the art and these inhibitors are contemplated to be used in  
combination with the present compounds. Such inhibitors  
include, but are not limited to, boroarginine derivatives,  
buropeptides, heparins, hirudin and argatroban, including  
pharmaceutically acceptable salts and prodrugs thereof.  
15 Boroarginine derivatives and buropeptides include N-acetyl  
and peptide derivatives of boronic acid, such as C-terminal  
a-aminoboronic acid derivatives of lysine, ornithine,  
arginine, homoarginine and corresponding isothiuronium  
analogs thereof. The term hirudin, as used herein, includes  
20 suitable derivatives or analogs of hirudin, referred to  
herein as hirulogs, such as disulfatohirudin. Buropeptide  
thrombin inhibitors include compounds described in Kettner  
et al., U.S. 5,187,157 and EP 293 881 A2, the disclosures of  
which are hereby incorporated herein by reference. Other  
25 suitable boroarginine derivatives and buropeptide thrombin  
inhibitors include those disclosed in WO92/07869 and EP  
471,651 A2, the disclosures of which are hereby incorporated  
herein by reference.

The term thrombolytics (or fibrinolytic) agents (or  
30 thrombolytics or fibrinolytics), as used herein, denotes  
agents that lyse blood clots (thrombi). Such agents include  
tissue plasminogen activator, anistreplase, urokinase or  
streptokinase, including pharmaceutically acceptable salts  
or prodrugs thereof. The term anistreplase, as used herein,  
35 refers to anisoylated plasminogen streptokinase activator  
complex, as described, for example, in EP 028,489, the  
disclosure of which is hereby incorporated herein by  
reference herein. The term urokinase, as used herein, is  
intended to denote both dual and single chain urokinase, the  
40 latter also being referred to herein as prourokinase.

5 Administration of the compounds of the present  
invention in combination with such additional therapeutic  
agent, may afford an efficacy advantage over the compounds  
and agents alone, and may do so while permitting the use of  
lower doses of each. A lower dosage minimizes the potential  
10 of side effects, thereby providing an increased margin of  
safety.

The compounds of the present invention are also useful  
as standard or reference compounds, for example as a quality  
standard or control, in tests or assays involving the  
15 inhibition of factor Xa. Such compounds may be provided in  
a commercial kit, for example, for use in pharmaceutical  
research involving factor Xa. For example, a compound of  
the present invention could be used as a reference in an  
assay to compare its known activity to a compound with an  
20 unknown activity. This would ensure the experimenter that  
the assay was being performed properly and provide a basis  
for comparison, especially if the test compound was a  
derivative of the reference compound. When developing new  
assays or protocols, compounds according to the present  
25 invention could be used to test their effectiveness.

The compounds of the present invention may also be used  
in diagnostic assays involving factor Xa. For example, the  
presence of factor Xa in an unknown sample could be  
determined by addition of chromogenic substrate S2222 to a  
30 series of solutions containing test sample and optionally  
one of the compounds of the present invention. If  
production of pNA is observed in the solutions containing  
test sample, but not in the presence of a compound of the  
present invention, then one would conclude factor Xa was  
35 present.

#### Dosage and Formulation

The compounds of this invention can be  
administered in such oral dosage forms as tablets, capsules  
40 (each of which includes sustained release or timed release  
formulations), pills, powders, granules, elixirs, tinctures,



5 suspensions, syrups, and emulsions. They may also be  
administered in intravenous (bolus or infusion),  
intraperitoneal, subcutaneous, or intramuscular form, all  
using dosage forms well known to those of ordinary skill in  
the pharmaceutical arts. They can be administered alone,  
10 but generally will be administered with a pharmaceutical  
carrier selected on the basis of the chosen route of  
administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present  
invention will, of course, vary depending upon known  
15 factors, such as the pharmacodynamic characteristics of the  
particular agent and its mode and route of administration;  
the species, age, sex, health, medical condition, and weight  
of the recipient; the nature and extent of the symptoms; the  
kind of concurrent treatment; the frequency of treatment;  
20 the route of administration, the renal and hepatic function  
of the patient, and the effect desired. A physician or  
veterinarian can determine and prescribe the effective  
amount of the drug required to prevent, counter, or arrest  
the progress of the thromboembolic disorder.

25 By way of general guidance, the daily oral dosage of  
each active ingredient, when used for the indicated effects,  
will range between about 0.001 to 1000 mg/kg of body weight,  
preferably between about 0.01 to 100 mg/kg of body weight  
per day, and most preferably between about 1.0 to 20  
30 mg/kg/day. Intravenously, the most preferred doses will  
range from about 1 to about 10 mg/kg/minute during a  
constant rate infusion. Compounds of this invention may be  
administered in a single daily dose, or the total daily  
dosage may be administered in divided doses of two, three,  
35 or four times daily.

Compounds of this invention can be administered in  
intranasal form via topical use of suitable intranasal  
vehicles, or via transdermal routes, using transdermal skin  
patches. When administered in the form of a transdermal  
40 delivery system, the dosage administration will, of course,

5 be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical  
10 carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a  
15 tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral  
20 administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring  
25 agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol,  
30 waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the  
35 like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a  
40 variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

5           Compounds of the present invention may also be coupled  
with soluble polymers as targetable drug carriers. Such  
polymers can include polyvinylpyrrolidone, pyran copolymer,  
polyhydroxypropylmethacrylamide-phenol,  
polyhydroxyethylaspartamidephenol, or polyethyleneoxide-  
10 polylysine substituted with palmitoyl residues.  
Furthermore, the compounds of the present invention may be  
coupled to a class of biodegradable polymers useful in  
achieving controlled release of a drug, for example,  
polylactic acid, polyglycolic acid, copolymers of polylactic  
15 and polyglycolic acid, polyepsilon caprolactone, polyhydroxy  
butyric acid, polyorthoesters, polyacetals,  
polydihydropyrans, polycyanoacylates, and crosslinked or  
amphiphathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for  
20 administration may contain from about 1 milligram to about  
100 milligrams of active ingredient per dosage unit. In  
these pharmaceutical compositions the active ingredient will  
ordinarily be present in an amount of about 0.5-95% by  
weight based on the total weight of the composition.

25           Gelatin capsules may contain the active ingredient and  
powdered carriers, such as lactose, starch, cellulose  
derivatives, magnesium stearate, stearic acid, and the like.  
Similar diluents can be used to make compressed tablets.  
Both tablets and capsules can be manufactured as sustained  
30 release products to provide for continuous release of  
medication over a period of hours. Compressed tablets can  
be sugar coated or film coated to mask any unpleasant taste  
and protect the tablet from the atmosphere, or enteric  
coated for selective disintegration in the gastrointestinal  
35 tract.

Liquid dosage forms for oral administration can contain  
coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous  
dextrose (glucose), and related sugar solutions and glycols  
40 such as propylene glycol or polyethylene glycols are  
suitable carriers for parenteral solutions. Solutions for

5 parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents.  
10 Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in  
15 Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

20 Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams  
25 magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement  
30 pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

Tablets may be prepared by conventional procedures so  
35 that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase  
40 palatability or delay absorption.

5        Injectable

A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution should be made isotonic with sodium chloride and sterilized.

10       Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of the present invention and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of the present invention are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of the present invention and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of the present invention and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

Where the compounds of the present invention are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of the present invention, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolytic agent when

5 administered alone may be reduced by about 70-80% when  
administered with a compound of the present invention.

Where two or more of the foregoing second therapeutic  
agents are administered with the compound of the present  
invention, generally the amount of each component in a  
10 typical daily dosage and typical dosage form may be reduced  
relative to the usual dosage of the agent when administered  
alone, in view of the additive or synergistic effect of the  
therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the  
15 potential exists for a chemical interaction between the  
combined active ingredients. For this reason, when the  
compound of the present invention and a second therapeutic  
agent are combined in a single dosage unit they are  
formulated such that although the active ingredients are  
20 combined in a single dosage unit, the physical contact  
between the active ingredients is minimized (that is,  
reduced). For example, one active ingredient may be enteric  
coated. By enteric coating one of the active ingredients,  
it is possible not only to minimize the contact between the  
25 combined active ingredients, but also, it is possible to  
control the release of one of these components in the  
gastrointestinal tract such that one of these components is  
not released in the stomach but rather is released in the  
intestines. One of the active ingredients may also be  
30 coated with a material that affects a sustained-release  
throughout the gastrointestinal tract and also serves to  
minimize physical contact between the combined active  
ingredients. Furthermore, the sustained-released component  
can be additionally enteric coated such that the release of  
35 this component occurs only in the intestine. Still another  
approach would involve the formulation of a combination  
product in which the one component is coated with a  
sustained and/or enteric release polymer, and the other  
component is also coated with a polymer such as a low-  
40 viscosity grade of hydroxypropyl methylcellulose (HPMC) or  
other appropriate materials as known in the art, in order to

5 further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

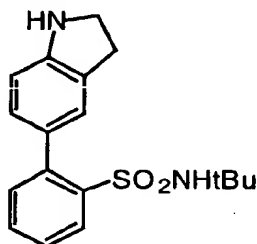
These as well as other ways of minimizing contact between the components of combination products of the  
10 present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Other features of the invention will become apparent in  
15 the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

#### EXAMPLES

##### Example 1

20 **2-(2,3-Dihydro-1H-indol-5-yl)-N-(1,1-dimethylethyl)benzenesulfonamide**

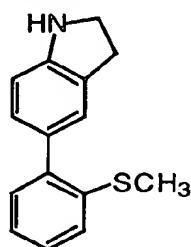


25 A solution of 5-indoleboronic acid (2.9 g, 18 mmol), prepared according to the procedure of Yang (*Heterocycles* **1992**, 34, 1169) and 2-bromobenzyl-*tert*-butylsulfonyl amide (2.5 g, 18 mmol) in a mixture of ethylene glycol dimethyl ether (20 mL) and aqueous sodium carbonate (10 mL) was  
30 deoxygenated by a rapid stream of nitrogen applied to the system for 20 min, then treated with Pd(0) at once. The reaction was refluxed for 18h, cooled down, filtered through Celite® and washed with THF (20 mL). The filtrate was evaporated to dryness, taken up in water and extracted with  
35 EtOAc (3x). The EtOAc extracts were dried over sodium sulfate and concentrated. The crude residue was purified by

5 flash chromatography (hexane/EtOAc, 1:3) to afford 2-(1*H*-indol-5-yl)-*N*-(1,1-dimethylethyl)benzenesulfonamide (0.7 g, 12%).

The product (0.29 g, 0.9 mmol) was dissolved in acetic acid and treated with sodium cyanoborohydride (54 mg, 0.9 mmol). The reaction mixture was stirred for 4h, concentrated and purified through a plug of silica gel(hexane/EtOAc, 1:1) to afford the title product (232 mg, 77%). LRMS (ES<sup>+</sup>): 331.1 (M+H)<sup>+</sup>.

15

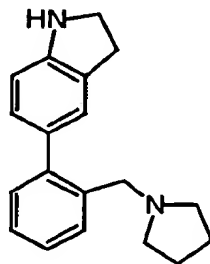
**Example 2****2,3-Dihydro-5-[2-(methylthio)phenyl]-1*H*-indole**

A solution of 5-indoleboronic acid (2.0 g, 12 mmol) and 2-bromothioanisole (1.6 mL, 12 mmol) in a mixture of ethylene glycol dimethyl ether (20 mL) and aqueous sodium carbonate (10 mL) was deoxygenated by a rapid stream of nitrogen applied to the system for 20 min, then treated with Pd(0) at once. The reaction was refluxed for 18h, cooled down, filtered through Celite® and washed with THF (20 mL). The filtrate evaporated to dryness, taken up in water and extracted with EtOAc (3x). The EtOAc extracts were dried over sodium sulfate and concentrated. The crude residue was purified by flash chromatography (hexane/EtOAc, 1:3) to afford 5-[2-(methylthio)phenyl]-1*H*-indole (1.5 g, 52%).

The product (0.35 g, 1.5 mmol) was dissolved in acetic acid and treated with sodium cyanoborohydride (94 mg, 1.5 mmol). The reaction mixture was stirred for 4h, concentrated and purified through a plug of silica gel(hexane/EtOAc, 1:1) to afford the desired product (170mg, 46%). LRMS (ES<sup>+</sup>): 331.1 (M+H)<sup>+</sup>.



5

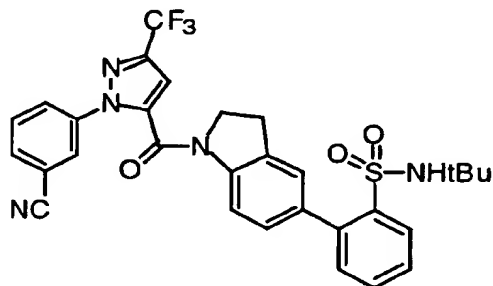
**Example 3****2,3-Dihydro-5-[2-(1-pyrrolidinymethyl)phenyl]-1H-indole**

10 A mixture of N-BOC-indole (2.0 g, 6.7 mmol) and 2-formyl benzene boronic acid (1 g, 6.7 mmol) was diluted with THF (20 mL) and 2M sodium carbonate (10 mL), then deoxygenated by a rapid stream of nitrogen applied to the system for 20 min, followed by treatment with Pd(0). The  
15 reaction was refluxed for 18h, cooled down, filtered through Celite® and washed with THF (20 mL). The filtrate evaporated to dryness, taken up in water, and extracted with EtOAc (3x). The EtOAc extracts were dried over sodium sulfate and concentrated. The crude residue (1 g, 1.5 mmol)  
20 was treated with sodium borohydride (0.14 g, 1.5 mmol) and pyrrolidine (0.3 mL, 1.5 mmol). The reaction mixture was stirred for 18h, diluted with ice water and extracted with EtOAc. Ethyl acetate extracts were dried over sodium sulfate and concentrated. The crude residue was purified by  
25 flash chromatography (hexane/EtOAc, 1:3) to afford an intermediate indole (0.27 g), that was treated with TFA (10 mL) and sodium cyanoborohydride (43 mg, 0.7 mmol). The reaction mixture was stirred for 4h, concentrated and purified through a plug of silica gel(hexane/EtOAc, 1:1) to  
30 afford the desired product (0.25 g, 29% over last 2 steps). LRMS (ES+): 279.2 (M+H)<sup>+</sup>.

5

**Example 4**

**1-[[1-[3-Cyanophenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indol**



10

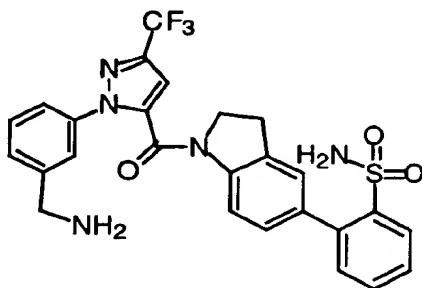
To the solution of 3-(trifluoromethyl)-1-(3-cyanophenyl)-1H-pyrazolecarboxylic acid (0.2 g, 0.6 mmol) in dry acetonitrile (10 mL) was added thionyl chloride (0.37 g, 1.8 mmol). The reaction mixture was warmed up to 50°C for 1h. The solvent and excess thionyl chloride were removed under reduced pressure and dried on a vacuum pump over 18h. This residue was dissolved in THF and treated with a mixture of 2-(2,3-dihydro-1H-indol-5-yl)-N-(1,1-dimethylethyl)benzenesulfonamide from Example 1 (0.3 g, 0.8 mmol) in THF (5 mL) and NaH (72 mg, 1.6 mmol). The reaction mixture was allowed to stir at ambient temperature for 0.5h, then quenched with water and extracted with EtOAc (3x). Ethyl acetate extracts were dried over sodium sulfate and concentrated. The crude residue was purified by flash chromatography (hexane/EtOAc, 1:3) to afford the title product (0.38 g, 92%). LRMS (ES<sup>+</sup>): 593.2 (M+H)<sup>+</sup>.

25

5

**Example 5**

**1-[[1-[3-(Aminomethyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole**



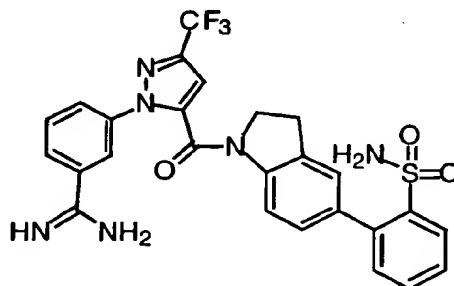
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1-[[1-[3-Cyanophenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole (0.2 g, 0.34 mmol), prepared according to Example 4, was reduced under an atmosphere of hydrogen gas (55 psi) in methanol (5 mL) and trifluoroacetic acid in the presence of 10% palladium on carbon catalyst for 18h at ambient temperature. The reaction mixture was filtered through a pad of Celite® and washed with methanol (3x). This product was treated with trifluoroacetic acid (1 mL) at 80°C over 1h, then purified by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% of trifluoroacetic acid on a reverse phase C18 (60 angstrom) column to give the title product (28 mg, 15%). LRMS (ES+): 598.2 (M+H)<sup>+</sup>.

25

**Example 6**

**1-[[1-[3-(Aminoiminomethyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole**

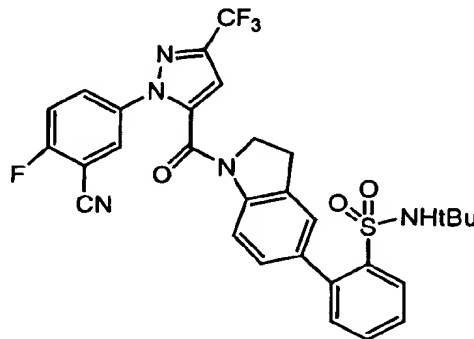


5

1-[[1-[3-Cyanophenyl]-3(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole (0.2 g, 0.34 mmol), prepared according to Example 4, was placed in a mixture of chloroform and methanol (1:1, 10 mL), cooled to 0°C and a stream of HCl gas was passed through the solution for 15 min. The resultant mixture was sealed and let to stand for 18h at ambient temperature, then concentrated, diluted with methanol (5 mL), and treated with ammonium carbonate (1g, excess). The resultant mixture was sealed and allowed to stand over 18h at ambient temperature, then concentrated. The residue was purified by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% of trifluoroacetic acid on a reverse phase C18 (60 angstrom) column to give the title product (30 mg, 16%). LRMS (ES<sup>+</sup>): 555.1 (M+H)<sup>+</sup>.

#### Example 7

1-[[1-[3-Cyano-4-fluorophenyl]-3(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole

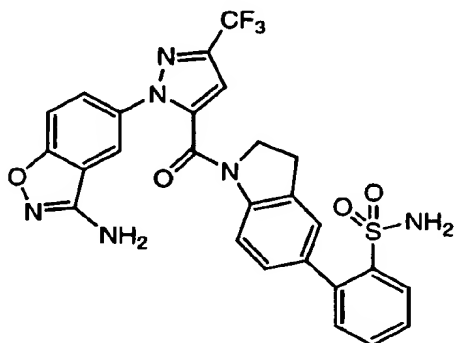


1-[[1-[3-Cyano-4-fluorophenyl]-3(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole was prepared according to Example 4, LRMS (ES<sup>+</sup>): 610.1 (M+H)<sup>+</sup>.

5

**Exempl 8**

**1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl-1H-pyrazol-5-yl)carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole**



10

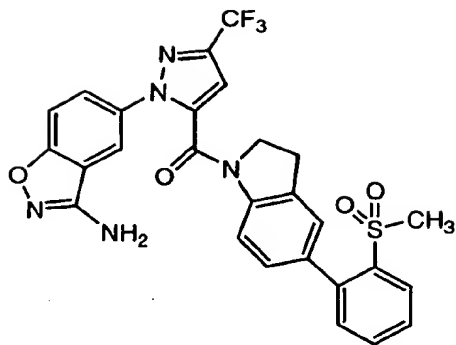
To a solution of acetone oxime (0.13 g, 1.8 mmol) in DMF (6 mL) was added 1-[[1-[3-cyano-4-fluorophenyl]-3(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole (0.35 g, 0.57 mmol), prepared according to Example 7, in DMF (2mL). The reaction was stirred at room temperature for 5h, then partitioned between HCl(5%) and EtOAc, washed with water and brine, dried over sodium sulfate and concentrated. The crude residue was purified by flash chromatography (hexane/EtOAc, 1:3) to afford an intermediate (0.34 g, 89%). This product was dissolved in ethanol(5 mL) and HCl(20%, 5 mL). The reaction mixture was stirred at 80°C for 3h, cooled down and filtered. The precipitate was purified by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% of trifluoroacetic acid on a reverse phase C18 (60 angstrom) column to give (42 mg, 13%). LRMS (ES+): 568.2 (M+H)<sup>+</sup>.

25

**Example 9**

**1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[2-(methylsulfonyl)phenyl]-1H-indole**

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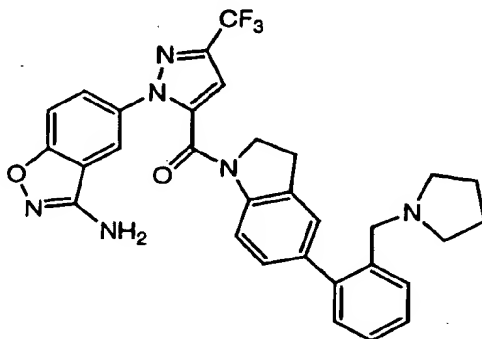


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1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[2-(methylsulfonyl)phenyl]-1H-indole was prepared according to Example 8, followed by MCPBA oxidation (MCPBA (2 eq.), methylene chloride, ambient temperature, 20h), LRMS (ES<sup>+</sup>): 567.6 (M+H)<sup>+</sup>.

#### Example 10

1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[2-(1-pyrrolidinylmethyl)phenyl]-1H-indole

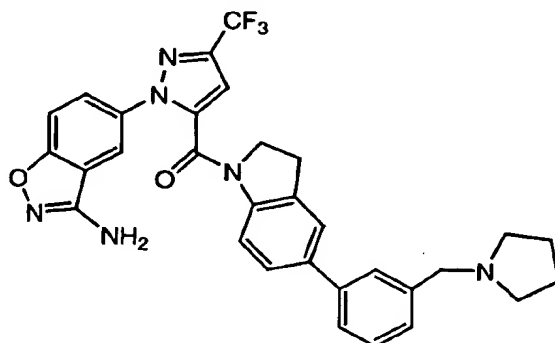


1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[2-(1-pyrrolidinylmethyl)phenyl]-1H-indole was prepared according to Example 8, LRMS (ES<sup>+</sup>): 568.5 (M+H)<sup>+</sup>.

5

**Example 11**

**1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[3-(1-pyrrolidinylmethyl)phenyl]-1H-indole**



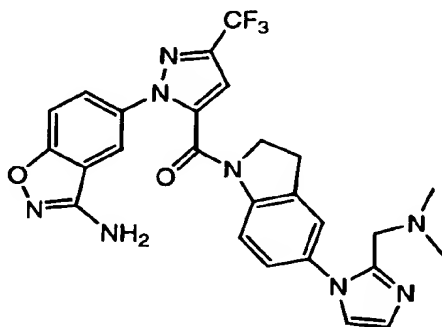
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1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[3-(1-pyrrolidinylmethyl)phenyl]-1H-indole was prepared according to Examples 3 and 8, LRMS (ES<sup>+</sup>): 568.5 (M+H)<sup>+</sup>.

15

**Example 12**

**1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[(2'-dimethylaminomethyl)imidazol-1-yl]-indoline**



20

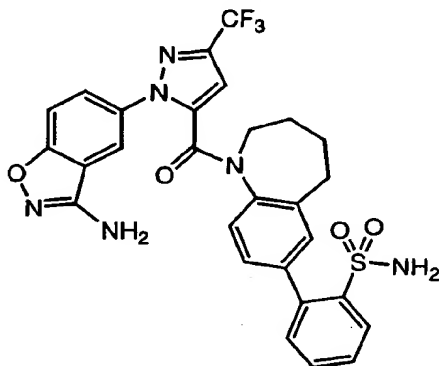
5-Bromoindoline (3.90 g, 19.7 mmol), (2'-dimethylaminomethyl)imidazole (2.95 g, 23.6 mmol), potassium carbonate (2.99 g, 21.7 mmol), 1,10-phenanthroline (177 mg, 5 mol%), and copper (I) iodide (187 mg, 5 mol %) were added together with 20 mL of DMSO. The mixture was degassed and then heated at 128°C under N<sub>2</sub> for 16h. The mixture was

5 cooled and then poured into water. It was extracted with EtOAc, washed with brine, dried over  $\text{MgSO}_4$ , and concentrated. The crude mixture purified by chromatography (eluted with EtOAc then 10 % MeOH in  $\text{CH}_2\text{Cl}_2$ ) to give 0.90 g of 5-[(2'-dimethylaminomethyl)imidazol-1-yl]indoline (45%). MS (ES+):  
10 243.2, M+H.

The title product was then prepared according to Examples 1, 4, and 8, LRMS (ES+): 537.5 (M+H)<sup>+</sup>.

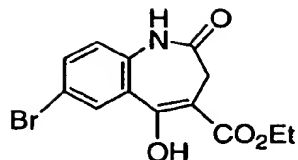
### Example 13

15 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3,4,5-tetrahydro-7-[2-(aminosulfonyl)phenyl]-benzazepine



20 2-Amino-5-bromobenzoic acid (24.7 g, 11.4 mol) was dissolved in 350 mL of ethanol and 2, and 5 mL of concentrated  $\text{H}_2\text{SO}_4$  was added. The mixture was refluxed under  $\text{N}_2$  for 12h. The solvent was removed and the residue was added with EtOAc. The mixture was extracted with 1N NaOH.  
25 The organic solution was washed with brine, dried over  $\text{MgSO}_4$ . It was concentrated and chromatographed with  $\text{CH}_2\text{Cl}_2$  to give 3.19 g of 2-amino-5-bromobenzoic acid, ethyl ester. MS (AP+): 243.9, 246, M+H.

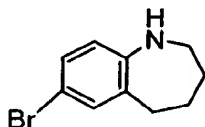




5 The above solid (3.18 g, 13.0 mmol) was dissolved in 50 mL of  $\text{CH}_2\text{Cl}_2$ . Triethylamine (1.91 mL, 13.7 mmol) was added followed by ethyl 4-chloro-4-oxobutyrates (1.86 mL, 13.1 mmol). The mixture was stirred at rt under  $\text{N}_2$  for 12h. It was then diluted with  $\text{CH}_2\text{Cl}_2$  and washed with  $\text{H}_2\text{O}$ , 1N HCl, 1N NaOH, and brine. The organic mixture was dried over  $\text{MgSO}_4$ ,  
 10 concentrated, and chromatographed with  $\text{CH}_2\text{Cl}_2$  to give 3.20 g of benzoic acid, 5-bromo-2-[(4-dioxo-4-propoxybutyl)amino]-ethyl ester. MS (AP+): 372, 379, M+H.

To a suspension of KH (4.00 g, 34.9 mmol) in 20 mL of  
 15 toluene at  $0^\circ\text{C}$  was added a solution of the above amide (2.17 g, 5.83 mmol) in 20 mL of toluene and 20 mL of DMF. After  $\text{H}_2$  evolution stopped, the reaction mixture was heated at  $70^\circ\text{C}$  for 3h. The mixture was cooled to rt and 5 mL of glacial acetic acid was added followed by 20 mL of  $\text{H}_2\text{O}$ . The  
 20 precipitate formed was filtered and air dried to give 0.93 g of the desired product.

The above solid (0.93 g, 2.85 mmol) was combined with  $\text{H}_2\text{O}$  (0.16 mL, 8.89 mmol) and DMSO (8 mL). The mixture was heated at  $150^\circ\text{C}$  for 3h under  $\text{N}_2$ . The mixture was poured into  
 25 water and extracted with EtOAc. The organic solution was washed with brine, dried over  $\text{MgSO}_4$ , concentrated, and chromatographed with 0-50% EtOAc in hexane to give 0.44 g of 7-bromo-3,4-dihydro-1H-1-benzazepine-2,5-dione. MS (AP+): 295, 297, M+H.



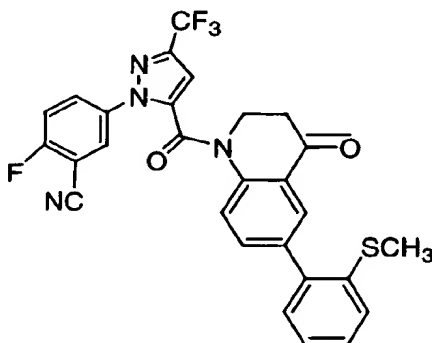
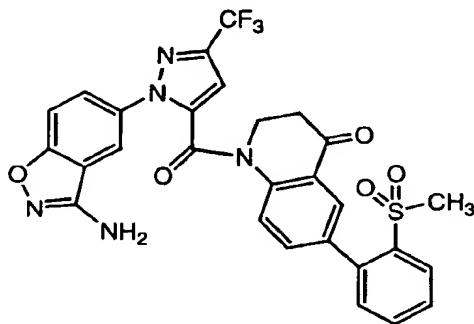
30 To a slurry of LAH (0.14 g, 3.69 mmol) in 10 mL of THF was added  $\text{AlCl}_3$  (0.46 g, 3.45 mmol) in two portions. The mixture was stirred at rt for 15 minutes and a solution of 7-bromo-3,4-dihydro-1H-1-benzazepine-2,5-dione (0.22 g, 0.87 mmol) in 10 mL of THF was added dropwise. The mixture was

5 then heated at 60°C for 12h. The reaction was cooled and quenched. It was extracted with EtOAc. The organic solution was washed with brine, dried over MgSO<sub>4</sub>, concentrated, and chromatographed with 20-100% EtOAc in hexane to give 0.07 g of 7-bromo-2,3,4,5-tetrahydro-1H-1-benzazepine. MS (AP<sup>+</sup>): 267, 269, M+H.

The title product was then prepared according to Examples 2 and 8. LRMS (ES<sup>+</sup>): 595.6 (M+H)<sup>+</sup>.

#### Example 14

15 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-6-[2-(methylsulfonyl)phenyl]-1H-quinolin-4-one

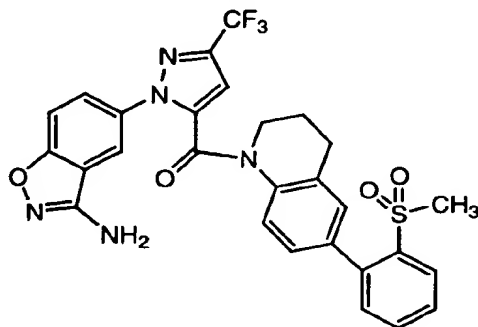


20 1-[[1-[3-Cyano-4-fluorophenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-6-bromo-2,3-dihydro-1H-quinolin-4-one] was prepared according to Example 4, LRMS (ES<sup>+</sup>): 494.1 (M+H)<sup>+</sup>. 1-[[1-[3-Cyano-4-fluorophenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-6-[2-(methylthio)phenyl]-1H-quinolin-4-one was then prepared according to Example 2, LRMS (ES<sup>+</sup>): 537.1 (M+H)<sup>+</sup>. The title

5 product was then prepared according to Example 9, LRMS  
(ES+): 582.1 (M+H)<sup>+</sup>.

#### Example 15

10 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-6-[2-  
(methylsulfonyl)phenyl]-1H-quinoline

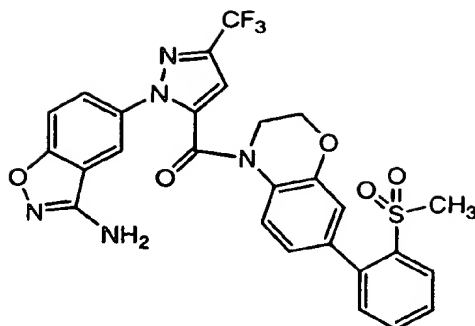


15 A solution of 6-bromo-2,3-dihydro-1H-quinolin-3-one  
(0.05 g, 0.219 mmol) in THF (20 mL) and aqueous sodium  
carbonate (5 mL) was treated with aluminum trichloride  
(0.116g, 0.9 mmol) and lithium aluminum hydride (33mg,  
0.9mmol) The reaction was refluxed for 18h. and cooled  
down. The filtrate evaporated to dryness, taken up in water  
20 and extracted with EtOAc (3x). Ethyl acetate extracts were  
dried over sodium sulfate and concentrated. The crude  
residue was purified by flash chromatography (hexane/EtOAc,  
1:3) to afford 6-bromo-2,3-dihydro-1H-quinoline (0.040g,  
87%). LRMS (ES+): 211.3 (M+H)<sup>+</sup>.

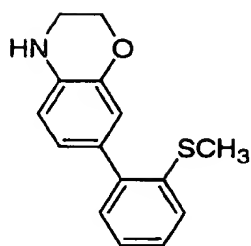
25 The title product was then prepared according to  
Example 14, LRMS (ES+): 568.2 (M+H)<sup>+</sup>.

#### Example 16

30 4-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-7-[2-  
(methylsulfonyl)phenyl]-2H-1,4-benzoxazine



5



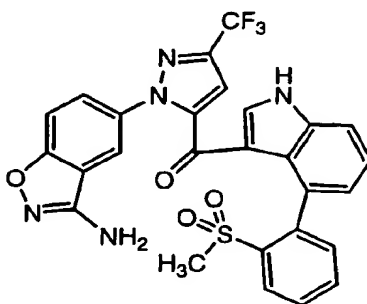
A solution of 7-bromo-1,4-benzoxazin-3-one (0.5 g, 2.2 mmol) and thioanisole-2-boronic acid (0.74g, 2.2 mmol) in a mixture of ethylene glycol dimethyl ether (20 mL) and aqueous sodium carbonate (10 mL) was deoxygenated by a rapid stream of nitrogen applied to the system for 20 min, then treated with Pd(0) at once. The reaction was refluxed for 18h, cooled down, filtered through Celite® and washed with THF (20 mL). The filtrate evaporated to dryness, taken up in water and extracted with EtOAc (3x). Ethyl acetate extracts were dried over sodium sulfate and concentrated. The crude residue was purified by flash chromatography (hexane/EtOAc, 1:3) to afford 2,3-dihydro-7-[2-(methylthio)phenyl]-1,4-benzoxazin-3-one (0.43 g, 72%). The product (0.2 g, 0.37 mmol) was dissolved in THF and treated with lithium aluminum hydride (56mg, 0.8 mmol). The reaction mixture was refluxed for 1h, concentrated and purified by a plug of silica gel (hexane/EtOAc, 1:1) to afford 2,3-dihydro-7-[2-(methylthio)phenyl]-1,4-benzoxazine (135g, 71%). LRMS (ES<sup>+</sup>): 258.4 (M+H)<sup>+</sup>.

The title product was then prepared according to Example 14, LRMS (ES<sup>+</sup>): 570.2 (M+H)<sup>+</sup>.

5

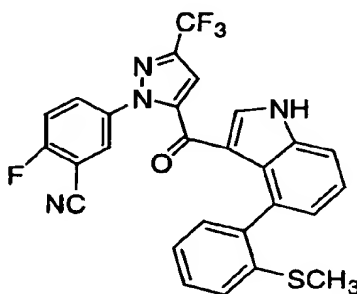
**Example 17**

**3-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-4-[2-(methylsulfonyl)phenyl]indole**



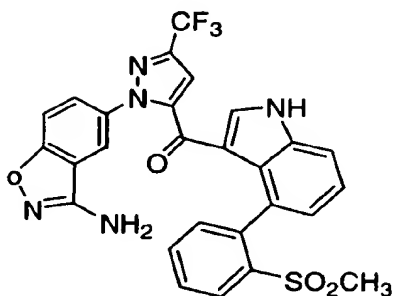
10

To the solution of 3-(trifluoromethyl)-1-(3-cyano-4-



fluorophenyl)-1H-pyrazolecarboxylic acid (0.3 g, 0.9 mmol) in dry acetonitrile (10 mL) was added thionyl chloride (0.74 g, 3.6 mmol). The reaction mixture was warmed up to 50°C for 1h. The solvent and excess thionyl chloride were removed under reduced pressure. The resulting material was dried on a vacuum pump for 18h. This residue was dissolved in THF and treated with a mixture of 4-[2-(methylthio)phenyl]indole (prepared according to Example 2) (0.3 g, 0.8 mmol) in methylene chloride (5 mL) and aluminum trichloride (135 mg, 1.1 mmol). The reaction mixture was allowed to stir at ambient temperature for 5h, then quenched with water and extracted with EtOAc (3x). EtOAc extracts were dried over sodium sulfate and concentrated. The crude residue was purified by flash chromatography (hexane/EtOAc, 1:3) to afford 1-[[1-[3-cyano-4-fluorophenyl]-3(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-4-[2-(methylthio)phenyl]-3-indole (0.17 g, 34%). LRMS (ES<sup>+</sup>): 521.2 (M+H)<sup>+</sup>.

5 The title product was then prepared according to



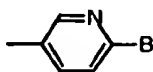
Example 9, LRMS (ES<sup>+</sup>): 501.4 (M+H)<sup>+</sup>.

5        The following tables contain representative examples of the present invention. Each entry in each table is intended to be paired with each formulae at the start of the table. For example, in Tables 1 and 2, example 1 is intended to be paired with each of the formulae.

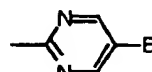
10       The following nomenclature is intended for group A in the following tables.



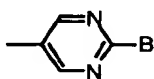
2-pyridyl



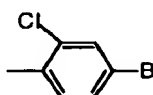
3-pyridyl



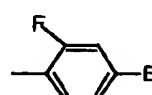
2-pyrimidyl



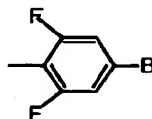
5-pyrimidyl



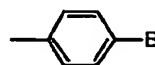
2-Cl-phenyl



2-F-phenyl



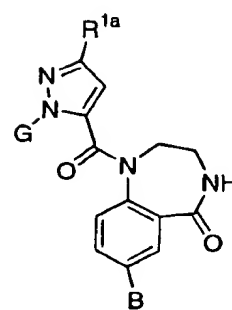
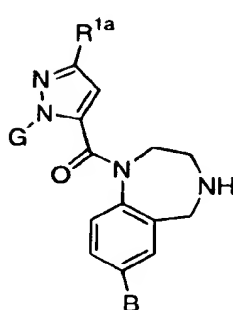
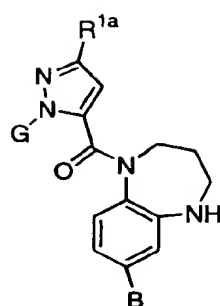
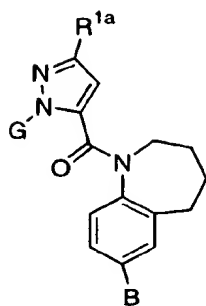
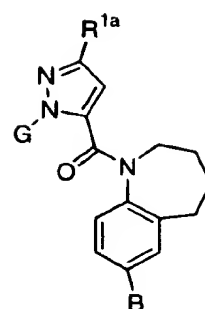
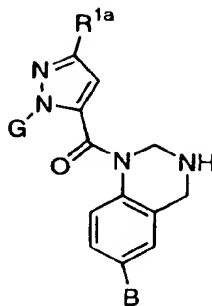
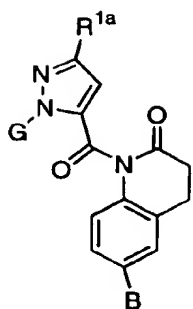
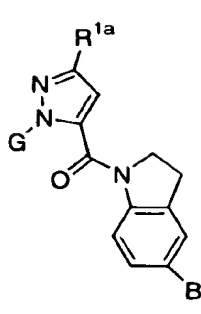
2,6-diF-phenyl



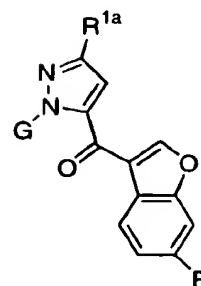
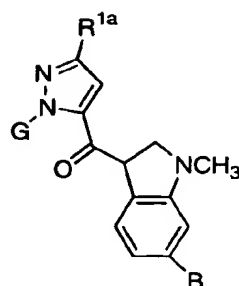
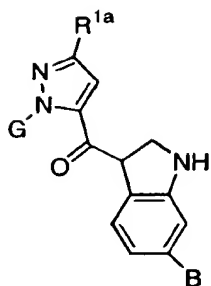
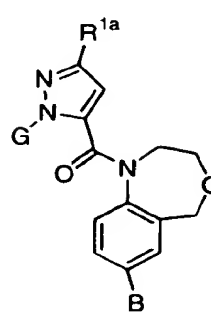
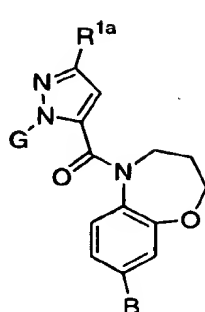
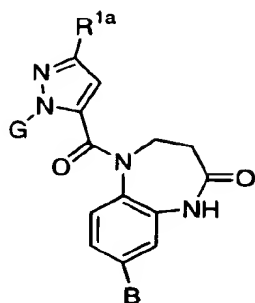
phenyl

5

Table 1



10



15 G is selected from:  
4-(methoxy)phenyl;



- 5        2-(aminomethyl)phenyl;  
          3-(aminomethyl)phenyl;  
          2-(aminomethyl)-3-fluorophenyl;  
          2-(aminomethyl)-4-fluorophenyl;  
          2-(aminomethyl)-5-fluorophenyl;  
 10       2-(aminomethyl)-6-fluorophenyl;  
          3-amino-phthalazin-5-yl;  
          3-amino-phthalazin-6-yl;  
          1-aminoisoquinolin-7-yl;  
          4-aminoquinazol-6-yl;  
 15       3-aminobenzisoxazol-5-yl; and,  
          3-aminoisobenzazol-5-yl;

Ex#	R1a	B
1.	CH3	2-(aminosulfonyl)phenyl
2.	CH3	2-(methylaminosulfonyl)phenyl
3.	CH3	1-pyrrolidinocarbonyl
4.	CH3	2-(methylsulfonyl)phenyl
5.	CH3	2-(N,N-dimethylaminomethyl)phenyl
6.	CH3	2-(N-pyrrolidinylmethyl)phenyl
7.	CH3	1-methyl-2-imidazolyl
8.	CH3	2-methyl-1-imidazolyl
9.	CH3	2-(dimethylaminomethyl)-1-imidazolyl
10.	CH3	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
11.	CH3	2-(N-(cyclobutyl)-aminomethyl)phenyl
12.	CH3	2-(N-(cyclopentyl)-aminomethyl)phenyl
13.	CH3	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
14.	CH3	2-(isopropylaminomethyl)phenyl
15.	CH3	4-azabenzimidazol-1-yl
16.	CH3	5-azabenzimidazol-1-yl
17.	CH3	6-azabenzimidazol-1-yl
18.	CH3	7-azabenzimidazol-1-yl
19.	CH2CH3	2-(aminosulfonyl)phenyl
20.	CH2CH3	2-(methylaminosulfonyl)phenyl
21.	CH2CH3	1-pyrrolidinocarbonyl
22.	CH2CH3	2-(methylsulfonyl)phenyl
23.	CH2CH3	2-(N,N-dimethylaminomethyl)phenyl
24.	CH2CH3	2-(N-pyrrolidinylmethyl)phenyl
25.	CH2CH3	1-methyl-2-imidazolyl
26.	CH2CH3	2-methyl-1-imidazolyl
27.	CH2CH3	2-(dimethylaminomethyl)-1-imidazolyl
28.	CH2CH3	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
29.	CH2CH3	2-(N-(cyclobutyl)-aminomethyl)phenyl
30.	CH2CH3	2-(N-(cyclopentyl)-aminomethyl)phenyl
31.	CH2CH3	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
32.	CH2CH3	2-(isopropylaminomethyl)phenyl
33.	CH2CH3	4-azabenzimidazol-1-yl
34.	CH2CH3	5-azabenzimidazol-1-yl

35.	CH <sub>2</sub> CH <sub>3</sub>	6-azabenzimidazol-1-yl
36.	CH <sub>2</sub> CH <sub>3</sub>	7-azabenzimidazol-1-yl
37.	CF <sub>3</sub>	2-(aminosulfonyl)phenyl
38.	CF <sub>3</sub>	2-(methylaminosulfonyl)phenyl
39.	CF <sub>3</sub>	1-pyrrolidinocarbonyl
40.	CF <sub>3</sub>	2-(methysulfonyl)phenyl
41.	CF <sub>3</sub>	2-(N,N-dimethylaminomethyl)phenyl
42.	CF <sub>3</sub>	2-(N-pyrrolidinylmethyl)phenyl
43.	CF <sub>3</sub>	1-methyl-2-imidazolyl
44.	CF <sub>3</sub>	2-methyl-1-imidazolyl
45.	CF <sub>3</sub>	2-(dimethylaminomethyl)-1-imidazolyl
46.	CF <sub>3</sub>	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
47.	CF <sub>3</sub>	2-(N-(cyclobutyl)-aminomethyl)phenyl
48.	CF <sub>3</sub>	2-(N-(cyclopentyl)-aminomethyl)phenyl
49.	CF <sub>3</sub>	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
50.	CF <sub>3</sub>	2-(isopropylaminomethyl)phenyl
51.	CF <sub>3</sub>	4-azabenzimidazol-1-yl
52.	CF <sub>3</sub>	5-azabenzimidazol-1-yl
53.	CF <sub>3</sub>	6-azabenzimidazol-1-yl
54.	CF <sub>3</sub>	7-azabenzimidazol-1-yl
55.	SCH <sub>3</sub>	2-(aminosulfonyl)phenyl
56.	SCH <sub>3</sub>	2-(methylaminosulfonyl)phenyl
57.	SCH <sub>3</sub>	1-pyrrolidinocarbonyl
58.	SCH <sub>3</sub>	2-(methysulfonyl)phenyl
59.	SCH <sub>3</sub>	2-(N,N-dimethylaminomethyl)phenyl
60.	SCH <sub>3</sub>	2-(N-pyrrolidinylmethyl)phenyl
61.	SCH <sub>3</sub>	1-methyl-2-imidazolyl
62.	SCH <sub>3</sub>	2-methyl-1-imidazolyl
63.	SCH <sub>3</sub>	2-(dimethylaminomethyl)-1-imidazolyl
64.	SCH <sub>3</sub>	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
65.	SCH <sub>3</sub>	2-(N-(cyclobutyl)-aminomethyl)phenyl
66.	SCH <sub>3</sub>	2-(N-(cyclopentyl)-aminomethyl)phenyl
67.	SCH <sub>3</sub>	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
68.	SCH <sub>3</sub>	2-(isopropylaminomethyl)phenyl
69.	SCH <sub>3</sub>	4-azabenzimidazol-1-yl
70.	SCH <sub>3</sub>	5-azabenzimidazol-1-yl
71.	SCH <sub>3</sub>	6-azabenzimidazol-1-yl
72.	SCH <sub>3</sub>	7-azabenzimidazol-1-yl
73.	SOCH <sub>3</sub>	2-(aminosulfonyl)phenyl
74.	SOCH <sub>3</sub>	2-(methylaminosulfonyl)phenyl
75.	SOCH <sub>3</sub>	1-pyrrolidinocarbonyl
76.	SOCH <sub>3</sub>	2-(methysulfonyl)phenyl
77.	SOCH <sub>3</sub>	2-(N,N-dimethylaminomethyl)phenyl
78.	SOCH <sub>3</sub>	2-(N-pyrrolidinylmethyl)phenyl
79.	SOCH <sub>3</sub>	1-methyl-2-imidazolyl
80.	SOCH <sub>3</sub>	2-methyl-1-imidazolyl
81.	SOCH <sub>3</sub>	2-(dimethylaminomethyl)-1-imidazolyl
82.	SOCH <sub>3</sub>	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
83.	SOCH <sub>3</sub>	2-(N-(cyclobutyl)-aminomethyl)phenyl
84.	SOCH <sub>3</sub>	2-(N-(cyclopentyl)-aminomethyl)phenyl
85.	SOCH <sub>3</sub>	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
86.	SOCH <sub>3</sub>	2-(isopropylaminomethyl)phenyl
87.	SOCH <sub>3</sub>	4-azabenzimidazol-1-yl
88.	SOCH <sub>3</sub>	5-azabenzimidazol-1-yl

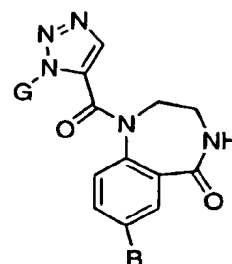
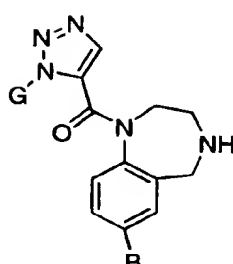
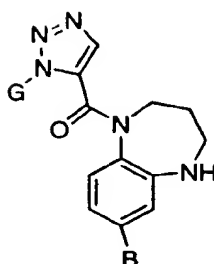
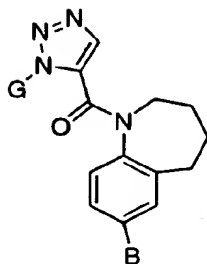
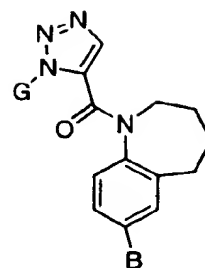
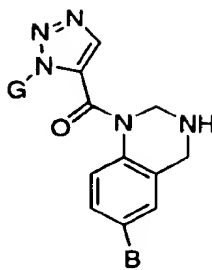
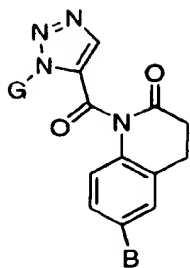
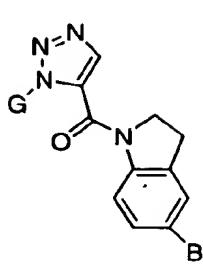
89.	SOCH3	6-azabenzimidazol-1-yl
90.	SOCH3	7-azabenzimidazol-1-yl
91.	SO2CH3	2-(aminosulfonyl)phenyl
92.	SO2CH3	2-(methylaminosulfonyl)phenyl
93.	SO2CH3	1-pyrrolidinocarbonyl
94.	SO2CH3	2-(methylsulfonyl)phenyl
95.	SO2CH3	2-(N,N-dimethylaminomethyl)phenyl
96.	SO2CH3	2-(N-pyrrolidinylmethyl)phenyl
97.	SO2CH3	1-methyl-2-imidazolyl
98.	SO2CH3	2-methyl-1-imidazolyl
99.	SO2CH3	2-(dimethylaminomethyl)-1-imidazolyl
100.	SO2CH3	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
101.	SO2CH3	2-(N-(cyclobutyl)-aminomethyl)phenyl
102.	SO2CH3	2-(N-(cyclopentyl)-aminomethyl)phenyl
103.	SO2CH3	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
104.	SO2CH3	2-(isopropylaminomethyl)phenyl
105.	SO2CH3	4-azabenzimidazol-1-yl
106.	SO2CH3	5-azabenzimidazol-1-yl
107.	SO2CH3	6-azabenzimidazol-1-yl
108.	SO2CH3	7-azabenzimidazol-1-yl
109.	Cl	2-(aminosulfonyl)phenyl
110.	Cl	2-(methylaminosulfonyl)phenyl
111.	Cl	1-pyrrolidinocarbonyl
112.	Cl	2-(methylsulfonyl)phenyl
113.	Cl	2-(N,N-dimethylaminomethyl)phenyl
114.	Cl	2-(N-pyrrolidinylmethyl)phenyl
115.	Cl	1-methyl-2-imidazolyl
116.	Cl	2-methyl-1-imidazolyl
117.	Cl	2-(dimethylaminomethyl)-1-imidazolyl
118.	Cl	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
119.	Cl	2-(N-(cyclobutyl)-aminomethyl)phenyl
120.	Cl	2-(N-(cyclopentyl)-aminomethyl)phenyl
121.	Cl	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
122.	Cl	2-(isopropylaminomethyl)phenyl
123.	Cl	4-azabenzimidazol-1-yl
124.	Cl	5-azabenzimidazol-1-yl
125.	Cl	6-azabenzimidazol-1-yl
126.	Cl	7-azabenzimidazol-1-yl
127.	F	2-(aminosulfonyl)phenyl
128.	F	2-(methylaminosulfonyl)phenyl
129.	F	1-pyrrolidinocarbonyl
130.	F	2-(methylsulfonyl)phenyl
131.	F	2-(N,N-dimethylaminomethyl)phenyl
132.	F	2-(N-pyrrolidinylmethyl)phenyl
133.	F	1-methyl-2-imidazolyl
134.	F	2-methyl-1-imidazolyl
135.	F	2-(dimethylaminomethyl)-1-imidazolyl
136.	F	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
137.	F	2-(N-(cyclobutyl)-aminomethyl)phenyl
138.	F	2-(N-(cyclopentyl)-aminomethyl)phenyl
139.	F	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
140.	F	2-(isopropylaminomethyl)phenyl
141.	F	4-azabenzimidazol-1-yl
142.	F	5-azabenzimidazol-1-yl

143.	F	6-azabenzimidazol-1-yl
144.	F	7-azabenzimidazol-1-yl
145.	CO <sub>2</sub> CH <sub>3</sub>	2-(N-pyrrolidinylmethyl)phenyl
146.	CO <sub>2</sub> CH <sub>3</sub>	1-methyl-2-imidazolyl
147.	CO <sub>2</sub> CH <sub>3</sub>	2-methyl-1-imidazolyl
148.	CO <sub>2</sub> CH <sub>3</sub>	2-(dimethylaminomethyl)-1-imidazolyl
149.	CO <sub>2</sub> CH <sub>3</sub>	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
150.	CO <sub>2</sub> CH <sub>3</sub>	2-(N-(cyclobutyl)-aminomethyl)phenyl
151.	CO <sub>2</sub> CH <sub>3</sub>	2-(N-(cyclopentyl)-aminomethyl)phenyl
152.	CO <sub>2</sub> CH <sub>3</sub>	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
153.	CO <sub>2</sub> CH <sub>3</sub>	2-(isopropylaminomethyl)phenyl
154.	CO <sub>2</sub> CH <sub>3</sub>	4-azabenzimidazol-1-yl
155.	CO <sub>2</sub> CH <sub>3</sub>	5-azabenzimidazol-1-yl
156.	CO <sub>2</sub> CH <sub>3</sub>	6-azabenzimidazol-1-yl
157.	CO <sub>2</sub> CH <sub>3</sub>	7-azabenzimidazol-1-yl
158.	CH <sub>2</sub> OCH <sub>3</sub>	2-(aminosulfonyl)phenyl
159.	CH <sub>2</sub> OCH <sub>3</sub>	2-(methylaminosulfonyl)phenyl
160.	CH <sub>2</sub> OCH <sub>3</sub>	1-pyrrolidinocarbonyl
161.	CH <sub>2</sub> OCH <sub>3</sub>	2-(methylsulfonyl)phenyl
162.	CH <sub>2</sub> OCH <sub>3</sub>	2-(N,N-dimethylaminomethyl)phenyl
163.	CH <sub>2</sub> OCH <sub>3</sub>	2-(N-pyrrolidinylmethyl)phenyl
164.	CH <sub>2</sub> OCH <sub>3</sub>	1-methyl-2-imidazolyl
165.	CH <sub>2</sub> OCH <sub>3</sub>	2-methyl-1-imidazolyl
166.	CH <sub>2</sub> OCH <sub>3</sub>	2-(dimethylaminomethyl)-1-imidazolyl
167.	CH <sub>2</sub> OCH <sub>3</sub>	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
168.	CH <sub>2</sub> OCH <sub>3</sub>	2-(N-(cyclobutyl)-aminomethyl)phenyl
169.	CH <sub>2</sub> OCH <sub>3</sub>	2-(N-(cyclopentyl)-aminomethyl)phenyl
170.	CH <sub>2</sub> OCH <sub>3</sub>	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
171.	CH <sub>2</sub> OCH <sub>3</sub>	2-(isopropylaminomethyl)phenyl
172.	CH <sub>2</sub> OCH <sub>3</sub>	4-azabenzimidazol-1-yl
173.	CH <sub>2</sub> OCH <sub>3</sub>	5-azabenzimidazol-1-yl
174.	CH <sub>2</sub> OCH <sub>3</sub>	6-azabenzimidazol-1-yl
175.	CH <sub>2</sub> OCH <sub>3</sub>	7-azabenzimidazol-1-yl
176.	CONH <sub>2</sub>	2-(aminosulfonyl)phenyl
177.	CONH <sub>2</sub>	2-(methylaminosulfonyl)phenyl
178.	CONH <sub>2</sub>	1-pyrrolidinocarbonyl
179.	CONH <sub>2</sub>	2-(methylsulfonyl)phenyl
180.	CONH <sub>2</sub>	2-(N,N-dimethylaminomethyl)phenyl
181.	CONH <sub>2</sub>	2-(N-pyrrolidinylmethyl)phenyl
182.	CONH <sub>2</sub>	1-methyl-2-imidazolyl
183.	CONH <sub>2</sub>	2-methyl-1-imidazolyl
184.	CONH <sub>2</sub>	2-(dimethylaminomethyl)-1-imidazolyl
185.	CONH <sub>2</sub>	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
186.	CONH <sub>2</sub>	2-(N-(cyclobutyl)-aminomethyl)phenyl
187.	CONH <sub>2</sub>	2-(N-(cyclopentyl)-aminomethyl)phenyl
188.	CONH <sub>2</sub>	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
189.	CONH <sub>2</sub>	2-(isopropylaminomethyl)phenyl
190.	CONH <sub>2</sub>	4-azabenzimidazol-1-yl
191.	CONH <sub>2</sub>	5-azabenzimidazol-1-yl
192.	CONH <sub>2</sub>	6-azabenzimidazol-1-yl
193.	CONH <sub>2</sub>	7-azabenzimidazol-1-yl
194.	CN	2-(aminosulfonyl)phenyl
195.	CN	2-(methylaminosulfonyl)phenyl
196.	CN	1-pyrrolidinocarbonyl

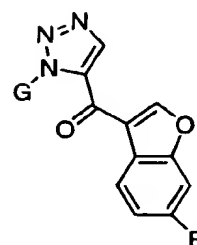
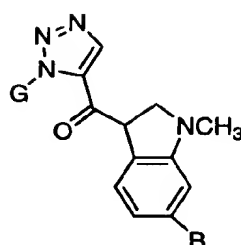
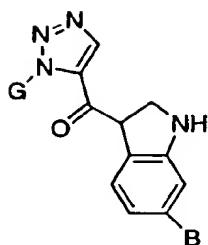
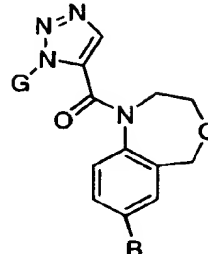
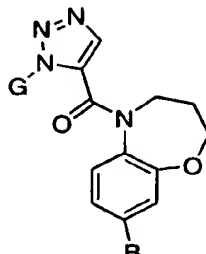
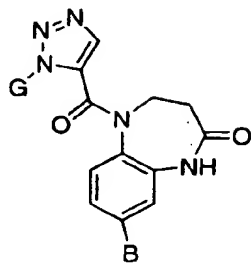
197.	CN	2-(methylsulfonyl)phenyl
198.	CN	2-(N,N-dimethylaminomethyl)phenyl
199.	CN	2-(N-pyrrolidinylmethyl)phenyl
200.	CN	1-methyl-2-imidazolyl
201.	CN	2-methyl-1-imidazolyl
202.	CN	2-(dimethylaminomethyl)-1-imidazolyl
203.	CN	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
204.	CN	2-(N-(cyclobutyl)-aminomethyl)phenyl
205.	CN	2-(N-(cyclopentyl)-aminomethyl)phenyl
206.	CN	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
207.	CN	2-(isopropylaminomethyl)phenyl
208.	CN	4-azabenzimidazol-1-yl
209.	CN	5-azabenzimidazol-1-yl
210.	CN	6-azabenzimidazol-1-yl
211.	CN	7-azabenzimidazol-1-yl
212.	CH <sub>2</sub> NH <sub>2</sub>	2-(N-pyrrolidinylmethyl)phenyl
213.	CH <sub>2</sub> NH <sub>2</sub>	1-methyl-2-imidazolyl
214.	CH <sub>2</sub> NH <sub>2</sub>	2-methyl-1-imidazolyl
215.	CH <sub>2</sub> NH <sub>2</sub>	2-(dimethylaminomethyl)-1-imidazolyl
216.	CH <sub>2</sub> NH <sub>2</sub>	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
217.	CH <sub>2</sub> NH <sub>2</sub>	2-(N-(cyclobutyl)-aminomethyl)phenyl
218.	CH <sub>2</sub> NH <sub>2</sub>	2-(N-(cyclopentyl)-aminomethyl)phenyl
219.	CH <sub>2</sub> NH <sub>2</sub>	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
220.	CH <sub>2</sub> NH <sub>2</sub>	2-(isopropylaminomethyl)phenyl
221.	CH <sub>2</sub> NH <sub>2</sub>	4-azabenzimidazol-1-yl
222.	CH <sub>2</sub> NH <sub>2</sub>	5-azabenzimidazol-1-yl
223.	CH <sub>2</sub> NH <sub>2</sub>	6-azabenzimidazol-1-yl
224.	CH <sub>2</sub> NH <sub>2</sub>	7-azabenzimidazol-1-yl
225.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	2-(aminosulfonyl)phenyl
226.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	2-(methylaminosulfonyl)phenyl
227.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	1-pyrrolidinocarbonyl
228.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	2-(methylsulfonyl)phenyl
229.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	2-(N,N-dimethylaminomethyl)phenyl
230.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	2-(N-pyrrolidinylmethyl)phenyl
231.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	1-methyl-2-imidazolyl
232.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	2-methyl-1-imidazolyl
233.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	2-(dimethylaminomethyl)-1-imidazolyl
234.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
235.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	2-(N-(cyclobutyl)-aminomethyl)phenyl
236.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	2-(N-(cyclopentyl)-aminomethyl)phenyl
237.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
238.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	2-(isopropylaminomethyl)phenyl
239.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	4-azabenzimidazol-1-yl
240.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	5-azabenzimidazol-1-yl
241.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	6-azabenzimidazol-1-yl
242.	CH <sub>2</sub> NHSO <sub>2</sub> CH <sub>3</sub>	7-azabenzimidazol-1-yl

5

Table 2



10



15 G is selected from:

4-(methoxy)phenyl;

2-(aminomethyl)phenyl;

3-(aminomethyl)phenyl;

2-(aminomethyl)-3-fluorophenyl;

20 2-(aminomethyl)-4-fluorophenyl;

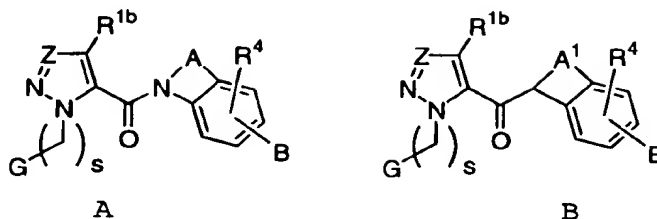
- 5        2-(aminomethyl)-5-fluorophenyl;  
          2-(aminomethyl)-6-fluorophenyl;  
          3-amino-phthalazin-5-yl;  
          3-amino-phthalazin-6-yl;  
          1-aminoisoquinolin-7-yl;  
 10       4-aminoquinazol-6-yl;  
          3-aminobenzisoxazol-5-yl; and,  
          3-aminoisobenzazol-5-yl;

Ex#	B
1.	2-(aminosulfonyl)phenyl
2.	2-(methylaminosulfonyl)phenyl
3.	1-pyrrolidinocarbonyl
4.	2-(methylsulfonyl)phenyl
5.	2-(N,N-dimethylaminomethyl)phenyl
6.	2-(N-pyrrolidinylmethyl)phenyl
7.	1-methyl-2-imidazolyl
8.	2-methyl-1-imidazolyl
9.	2-(dimethylaminomethyl)-1-imidazolyl
10.	2-(N-(cyclopropyl-methyl)aminomethyl)phenyl
11.	2-(N-(cyclobutyl)-aminomethyl)phenyl
12.	2-(N-(cyclopentyl)-aminomethyl)phenyl
13.	2-(N-(3-hydroxypyrrolidinyl)-methyl)phenyl
14.	2-(isopropylaminomethyl)phenyl
15.	4-azabenzimidazol-1-yl
16.	5-azabenzimidazol-1-yl
17.	6-azabenzimidazol-1-yl
18.	7-azabenzimidazol-1-yl

- 15       Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise that as specifically described herein.

5 **WHAT IS CLAIMED IS:**

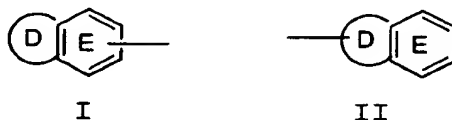
1. A compound of formula A or B:



10

or a stereoisomer or pharmaceutically acceptable salt thereof;

15 G is a group of formula I or II:



20 ring D is selected from  $-(CH_2)_3-$ ,  $-(CH_2)_4-$ ,  $-CH_2N=CH-$ ,  $-CH_2CH_2N=CH-$ , and a 5-6 membered aromatic system containing from 0-2 heteroatoms selected from the group N, O, and S;

25 ring D, when present, is substituted with 0-2 R, provided that when ring D is unsubstituted, it contains at least one heteroatom;

30 E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, substituted with 0-1 R;

R is selected from Cl, F, Br, I, OH,  $C_{1-3}$  alkoxy,  $NH_2$ ,  $NH(C_{1-3} \text{ alkyl})$ ,  $N(C_{1-3} \text{ alkyl})_2$ ,  $CH_2NH_2$ ,  $CH_2NH(C_{1-3} \text{ alkyl})$ ,  $CH_2N(C_{1-3} \text{ alkyl})_2$ ,  $CH_2CH_2NH_2$ ,  $CH_2CH_2NH(C_{1-3} \text{ alkyl})$ , and  $CH_2CH_2N(C_{1-3} \text{ alkyl})_2$ ;

35

alternatively, ring D is absent;



5

when ring D is absent, ring E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, and pyridazinyl, and ring E is substituted with  $R^a$  and  $R^b$ ;

10  $R^a$  is selected from H, F, Cl, Br, I,  $SR^3$ ,  $CO_2R^3$ ,  $NO_2$ ,  $(CH_2)_tOR^3$ ,  $C_{1-4}$  alkyl,  $OCF_3$ ,  $CF_3$ ,  $C(O)NR^7R^8$ , and  $(CR^8R^9)_tNR^7R^8$ ;

$R^b$  is selected from F, Cl, Br, I, OH,  $C_{1-3}$  alkoxy, CN,   
 15  $C(=NR^8)NR^7R^9$ ,  $NHC(=NR^8)NR^7R^9$ ,  $NR^8CH(=NR^7)$ ,  $C(O)NR^7R^8$ ,  $(CR^8R^9)_tNR^7R^8$ , SH,  $C_{1-3}$  alkyl-S,  $S(O)R^{3b}$ ,  $S(O)_2R^{3a}$ ,  $S(O)_2NR^2R^{2a}$ ,  $OCF_3$ , and a 5-6 membered heteroaromatic system containing from 1-4 heteroatoms selected from the group N, O, and S and substituted with  $R^c$ ;

20

alternatively,  $R^a$  and  $R^b$  combine to form methylenedioxy or ethylenedioxy;

$R^c$  is selected from OH, SH,  $C_{1-3}$  alkoxy,  $C_{1-3}$  thioalkoxy,  $NH_2$ ,   
 25  $NH(C_{1-3} \text{ alkyl})$ ,  $N(C_{1-3} \text{ alkyl})_2$ ,  $CH_2NH_2$ ,  $CH_2NH(C_{1-3} \text{ alkyl})$ ,  $CH_2N(C_{1-3} \text{ alkyl})_2$ ,  $CH_2CH_2NH_2$ ,  $CH_2CH_2NH(C_{1-3} \text{ alkyl})$ , and  $CH_2CH_2N(C_{1-3} \text{ alkyl})_2$ ;

Z is N or  $CR^{1a}$ ;

30

$R^{1a}$  is absent or selected from  $-(CH_2)_r-R^{1c}$ ,  $-CH=CH-R^{1c}$ ,  $NCH_2R^{1d}$ ,  $OCH_2R^{1d}$ ,  $SCH_2R^{1d}$ ,  $NH(CH_2)_2(CH_2)_tR^{1c}$ ,  $O(CH_2)_2(CH_2)_tR^{1c}$ , and  $S(CH_2)_2(CH_2)_tR^{1c}$ ;

35  $R^{1b}$  is absent or selected from  $-(CH_2)_r-R^{1c}$ ,  $-CH=CH-R^{1c}$ ,  $NCH_2R^{1d}$ ,  $OCH_2R^{1d}$ ,  $SCH_2R^{1d}$ ,  $NH(CH_2)_2(CH_2)_tR^{1c}$ ,  $O(CH_2)_2(CH_2)_tR^{1c}$ , and  $S(CH_2)_2(CH_2)_tR^{1c}$ ;

alternatively,  $R^{1a}$  and  $R^{1b}$ , when both are present, together   
 40 with the atoms to which they are attached form a 5-8 membered saturated, partially saturated or unsaturated

5 ring substituted with 0-2  $R^4$  and which contains from  
0-2 heteroatoms selected from the group consisting of  
N, O, and S;

10  $R^{1c}$  is selected from H,  $C_{1-3}$  alkyl, F, Cl, Br, I, -CN, -CHO,  
( $CF_2$ ) $_rCF_3$ , ( $CH_2$ ) $_rOR^2$ ,  $NR^2R^{2a}$ ,  $C(O)R^{2c}$ ,  $OC(O)R^2$ ,  
( $CF_2$ ) $_rCO_2R^{2c}$ ,  $S(O)_pR^{2b}$ ,  $NR^2(CH_2)_rOR^2$ ,  $CH(=NR^{2c})NR^2R^{2a}$ ,  
 $NR^2C(O)R^{2b}$ ,  $NR^2C(O)NHR^{2b}$ ,  $NR^2C(O)_2R^{2a}$ ,  $OC(O)NR^{2a}R^{2b}$ ,  
15  $C(O)NR^2R^{2a}$ ,  $C(O)NR^2(CH_2)_rOR^2$ ,  $SO_2NR^2R^{2a}$ ,  $NR^2SO_2R^{2b}$ ,  $C_{3-6}$   
carbocyclic residue substituted with 0-2  $R^4$ , and 5-10  
membered heterocyclic system containing from 1-4  
heteroatoms selected from the group consisting of N, O,  
and S substituted with 0-2  $R^4$ ;

20  $R^{1d}$  is selected from H,  $CH(CH_2OR^2)_2$ ,  $C(O)R^{2c}$ ,  $C(O)NR^2R^{2a}$ ,  
 $S(O)R^{2b}$ ,  $S(O)_2R^{2b}$ , and  $SO_2NR^2R^{2a}$ ;

25  $R^2$ , at each occurrence, is selected from H,  $CF_3$ ,  $C_{1-6}$  alkyl,  
benzyl,  $C_{3-6}$  carbocyclic residue substituted with 0-2  
 $R^{4b}$ , a  $C_{3-6}$  carbocyclic- $CH_2$ - residue substituted with  
0-2  $R^{4b}$ , and 5-6 membered heterocyclic system containing  
from 1-4 heteroatoms selected from the group consisting  
of N, O, and S substituted with 0-2  $R^{4b}$ ;

30  $R^{2a}$ , at each occurrence, is selected from H,  $CF_3$ ,  $C_{1-6}$  alkyl,  
benzyl,  $C_{3-6}$  carbocyclic residue substituted with 0-2  
 $R^{4b}$ , and 5-6 membered heterocyclic system containing  
from 1-4 heteroatoms selected from the group consisting  
of N, O, and S substituted with 0-2  $R^{4b}$ ;

35  $R^{2b}$ , at each occurrence, is selected from  $CF_3$ ,  $C_{1-4}$  alkoxy,  
 $C_{1-6}$  alkyl, benzyl,  $C_{3-6}$  carbocyclic residue substituted  
with 0-2  $R^{4b}$ , and 5-6 membered heterocyclic system  
containing from 1-4 heteroatoms selected from the group  
consisting of N, O, and S substituted with 0-2  $R^{4b}$ ;

40

5  $R^{2c}$ , at each occurrence, is selected from  $CF_3$ , OH,  $C_{1-4}$   
alkoxy,  $C_{1-6}$  alkyl, benzyl,  $C_{3-6}$  carbocyclic residue  
substituted with 0-2  $R^{4b}$ , and 5-6 membered heterocyclic  
system containing from 1-4 heteroatoms selected from  
the group consisting of N, O, and S substituted with  
10 0-2  $R^{4b}$ ;

alternatively,  $R^2$  and  $R^{2a}$ , together with the atom to which  
they are attached, combine to form a 5 or 6 membered  
saturated, partially saturated or unsaturated ring  
15 substituted with 0-2  $R^{4b}$  and containing from 0-1  
additional heteroatoms selected from the group  
consisting of N, O, and S;

$R^3$ , at each occurrence, is selected from H,  $C_{1-4}$  alkyl, and  
20 phenyl;

$R^{3a}$ , at each occurrence, is selected from H,  $C_{1-4}$  alkyl, and  
phenyl;

25  $R^{3b}$ , at each occurrence, is selected from H,  $C_{1-4}$  alkyl, and  
phenyl;

$R^{3c}$ , at each occurrence, is selected from  $C_{1-4}$  alkyl, and  
phenyl;

30 A is 2-5 membered linker substituted with 0-2  $R^4$  and  
selected from  $C_{2-4}$  alkylene,  $C_{2-4}$  alkenylene,  
 $(CH_2)_uO(CH_2)_u$ ,  $(CH_2)_uNH(CH_2)_u$ ,  $(CH_2)_uC(O)(CH_2)_u$ ,  
 $(CH_2)_uC(O)O(CH_2)_u$ ,  $(CH_2)_uOC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)NH(CH_2)_u$ ,  
35  $(CH_2)_uNHC(O)(CH_2)_u$ ,  $(CH_2)_uS(O)_p(CH_2)_u$ ,  $(CH_2)_uSO_2NH(CH_2)_u$ ,  
and  $(CH_2)_uNHSO_2(CH_2)_u$ , provided that A forms other than  
a N-O or N-S bond;

$A^1$  is 2-5 membered linker substituted with 0-2  $R^4$  and  
40 selected from  $C_{2-4}$  alkylene,  $C_{2-4}$  alkenylene,  
 $(CH_2)_uO(CH_2)_u$ ,  $(CH_2)_uNH(CH_2)_u$ ,  $(CH_2)_uC(O)(CH_2)_u$ ,

- 5 (CH<sub>2</sub>)<sub>u</sub>C(O)O(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>OC(O)(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>C(O)NH(CH<sub>2</sub>)<sub>u</sub>,  
(CH<sub>2</sub>)<sub>u</sub>NHC(O)(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>S(O)<sub>p</sub>(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>SO<sub>2</sub>NH(CH<sub>2</sub>)<sub>u</sub>,  
and (CH<sub>2</sub>)<sub>u</sub>NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>u</sub>, provided that A<sup>1</sup> forms other than  
a N-O or N-S bond;
- 10 alternatively, the CH<sub>2</sub>-A<sup>1</sup> group is replaced by a group  
selected from C=CH-NH, C=CH-O, and C=CH-S;
- B is selected from:  
X-Y, NR<sup>2</sup>R<sup>2a</sup>, C(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>C(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>,  
15 C<sub>3-10</sub> carbocyclic residue substituted with 0-2 R<sup>4a</sup>, and  
5-10 membered heterocyclic system containing from 1-4  
heteroatoms selected from the group consisting of N, O, and  
S substituted with 0-2 R<sup>4a</sup>;
- 20 X is selected from C<sub>1-4</sub> alkylene, -CR<sup>2</sup>(CR<sup>2</sup>R<sup>2b</sup>)(CH<sub>2</sub>)<sub>t</sub>-, -C(O)-,  
-C(=NR<sup>1d</sup>)-, -CR<sup>2</sup>(NR<sup>1d</sup>R<sup>2</sup>)-, -CR<sup>2</sup>(OR<sup>2</sup>)-, -CR<sup>2</sup>(SR<sup>2</sup>)-,  
-C(O)CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>C(O)-, -S(O)<sub>p</sub>-, -S(O)<sub>p</sub>CR<sup>2</sup>R<sup>2a</sup>-,  
-CR<sup>2</sup>R<sup>2a</sup>S(O)<sub>p</sub>-, -S(O)<sub>2</sub>NR<sup>2</sup>-, -NR<sup>2</sup>S(O)<sub>2</sub>-, -NR<sup>2</sup>S(O)<sub>2</sub>CR<sup>2</sup>R<sup>2a</sup>-,  
-CR<sup>2</sup>R<sup>2a</sup>S(O)<sub>2</sub>NR<sup>2</sup>-, -NR<sup>2</sup>S(O)<sub>2</sub>NR<sup>2</sup>-, -C(O)NR<sup>2</sup>-, -NR<sup>2</sup>C(O)-,  
25 -C(O)NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -NR<sup>2</sup>C(O)CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>C(O)NR<sup>2</sup>-,  
-CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>C(O)-, -NR<sup>2</sup>C(O)O-, -OC(O)NR<sup>2</sup>-, -NR<sup>2</sup>C(O)NR<sup>2</sup>-,  
-NR<sup>2</sup>-, -NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>-, O, -CR<sup>2</sup>R<sup>2a</sup>O-, and  
-OCR<sup>2</sup>R<sup>2a</sup>-;
- 30 Y is selected from:  
(CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, provided that X-Y do not form a N-N, O-N,  
or S-N bond,  
C<sub>3-10</sub> carbocyclic residue substituted with 0-2 R<sup>4a</sup>, and  
5-10 membered heterocyclic system containing from 1-4  
35 heteroatoms selected from the group consisting of N, O, and  
S substituted with 0-2 R<sup>4a</sup>;
- R<sup>4</sup>, at each occurrence, is selected from H, =O, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, F,  
Cl, Br, I, C<sub>1-4</sub> alkyl, -CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>,  
40 (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>2c</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>C(O)NR<sup>2</sup>R<sup>2a</sup>,  
CH(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, CH(=NS(O)<sub>2</sub>R<sup>5</sup>)NR<sup>2</sup>R<sup>2a</sup>, NHC(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>,

- 5         $C(O)NHC(=NR^2)NR^2R^{2a}$ ,  $SO_2NR^2R^{2a}$ ,  $NR^2SO_2NR^2R^{2a}$ ,  $NR^2SO_2-C_{1-4}$  alkyl,  $NR^2SO_2R^5$ ,  $S(O)_pR^5$ ,  $(CF_2)_rCF_3$ ,  $NCH_2R^{1d}$ ,  $OCH_2R^{1d}$ ,  $SCH_2R^{1d}$ ,  $N(CH_2)_2(CH_2)_tR^{1c}$ ,  $O(CH_2)_2(CH_2)_tR^{1c}$ , and  $S(CH_2)_2(CH_2)_tR^{1c}$ ;
- 10     $R^{4'}$ , at each occurrence, is selected from H, =O,  $(CH_2)_rOR^2$ , F, Cl, Br, I,  $C_{1-4}$  alkyl, -CN,  $NO_2$ ,  $(CH_2)_rNR^2R^{2a}$ ,  $(CH_2)_rC(O)R^{2c}$ ,  $NR^2C(O)R^{2b}$ ,  $C(O)NR^2R^{2a}$ ,  $SO_2NR^2R^{2a}$ , and  $(CF_2)_rCF_3$ ;
- 15     $R^{4a}$ , at each occurrence, is selected from H, =O,  $(CH_2)_rOR^2$ ,  $(CH_2)_r-F$ ,  $(CH_2)_r-Br$ ,  $(CH_2)_r-Cl$ , Cl, Br, F, I,  $C_{1-4}$  alkyl, -CN,  $NO_2$ ,  $(CH_2)_rNR^2R^{2a}$ ,  $(CH_2)_rC(O)R^{2c}$ ,  $NR^2C(O)R^{2b}$ ,  $C(O)NR^2R^{2a}$ ,  $C(O)NH(CH_2)_2NR^2R^{2a}$ ,  $NR^2C(O)NR^2R^{2a}$ ,  $CH(=NR^2)NR^2R^{2a}$ ,  $NHC(=NR^2)NR^2R^{2a}$ ,  $SO_2NR^2R^{2a}$ ,  $NR^2SO_2NR^2R^{2a}$ ,  $NR^2SO_2-C_{1-4}$  alkyl,  $C(O)NHSO_2-C_{1-4}$  alkyl,  $NR^2SO_2R^5$ ,  $S(O)_pR^5$ , and  $(CF_2)_rCF_3$ ;
- 20        alternatively, one  $R^{4a}$  is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-1  $R^5$ ;
- 25         $R^{4b}$ , at each occurrence, is selected from H, =O,  $(CH_2)_rOR^3$ , F, Cl, Br, I,  $C_{1-4}$  alkyl, -CN,  $NO_2$ ,  $(CH_2)_rNR^3R^{3a}$ ,  $(CH_2)_rC(O)R^3$ ,  $(CH_2)_rC(O)OR^{3c}$ ,  $NR^3C(O)R^{3a}$ ,  $C(O)NR^3R^{3a}$ ,  $NR^3C(O)NR^3R^{3a}$ ,  $CH(=NR^3)NR^3R^{3a}$ ,  $NR^3C(=NR^3)NR^3R^{3a}$ ,  $SO_2NR^3R^{3a}$ ,  $NR^3SO_2NR^3R^{3a}$ ,  $NR^3SO_2-C_{1-4}$  alkyl,  $NR^3SO_2CF_3$ ,  $NR^3SO_2$ -phenyl,  $S(O)_pCF_3$ ,  $S(O)_p-C_{1-4}$  alkyl,  $S(O)_p$ -phenyl, and  $(CF_2)_rCF_3$ ;
- 30         $R^5$ , at each occurrence, is selected from  $CF_3$ ,  $C_{1-6}$  alkyl, phenyl substituted with 0-2  $R^6$ , and benzyl substituted with 0-2  $R^6$ ;
- 35         $R^6$ , at each occurrence, is selected from H, OH,  $(CH_2)_rOR^2$ , halo,  $C_{1-4}$  alkyl, CN,  $NO_2$ ,  $(CH_2)_rNR^2R^{2a}$ ,  $(CH_2)_rC(O)R^{2b}$ ,
- 40

5            $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$ ,  $\text{NR}^2\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$ ,  $\text{CH}(=\text{NH})\text{NH}_2$ ,  $\text{NHC}(=\text{NH})\text{NH}_2$ ,  
           $\text{SO}_2\text{NR}^2\text{R}^{2a}$ ,  $\text{NR}^2\text{SO}_2\text{NR}^2\text{R}^{2a}$ , and  $\text{NR}^2\text{SO}_2\text{C}_{1-4}$  alkyl;

$\text{R}^7$ , at each occurrence, is selected from H, OH,  $\text{C}_{1-6}$  alkyl,  
           $\text{C}_{1-6}$  alkylcarbonyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{1-4}$  alkoxy carbonyl,  
10        $(\text{CH}_2)_n$ -phenyl,  $\text{C}_{6-10}$  aryloxy,  $\text{C}_{6-10}$  aryloxy carbonyl,  $\text{C}_{6-10}$   
          arylmethylcarbonyl,  $\text{C}_{1-4}$  alkylcarbonyloxy  $\text{C}_{1-4}$   
          alkoxy carbonyl,  $\text{C}_{6-10}$  arylcarbonyloxy  $\text{C}_{1-4}$   
          alkoxy carbonyl,  $\text{C}_{1-6}$  alkylaminocarbonyl,  
          phenylaminocarbonyl, and phenyl  $\text{C}_{1-4}$  alkoxy carbonyl;

15        $\text{R}^8$ , at each occurrence, is selected from H,  $\text{C}_{1-6}$  alkyl and  
           $(\text{CH}_2)_n$ -phenyl;

          alternatively,  $\text{R}^7$  and  $\text{R}^8$  combine to form a 5 or 6 membered  
20       saturated, ring which contains from 0-1 additional  
          heteroatoms selected from the group consisting of N, O,  
          and S;

$\text{R}^9$ , at each occurrence, is selected from H,  $\text{C}_{1-6}$  alkyl and  
25        $(\text{CH}_2)_n$ -phenyl;

          n, at each occurrence, is selected from 0, 1, 2, and 3;

          m, at each occurrence, is selected from 0, 1, and 2;

30       p, at each occurrence, is selected from 0, 1, and 2;

          r, at each occurrence, is selected from 0, 1, 2, and 3;

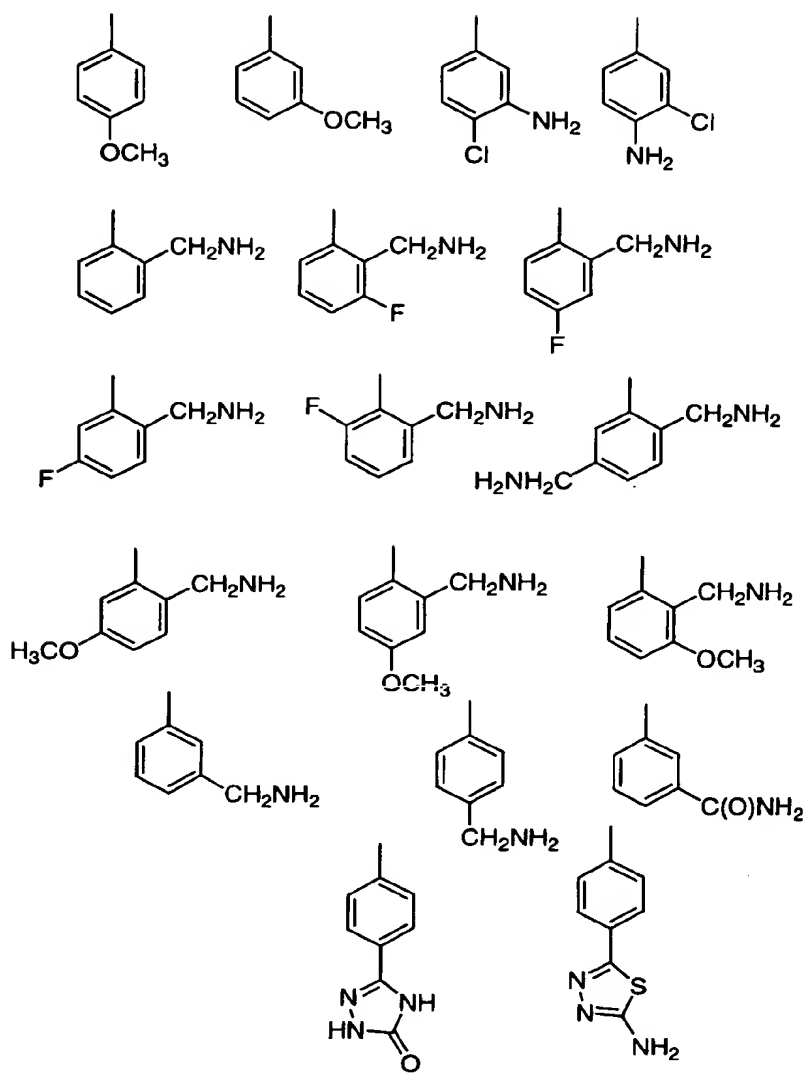
35       s, at each occurrence, is selected from 0, 1, and 2;

          t, at each occurrence, is selected from 0, 1, 2, and 3; and,

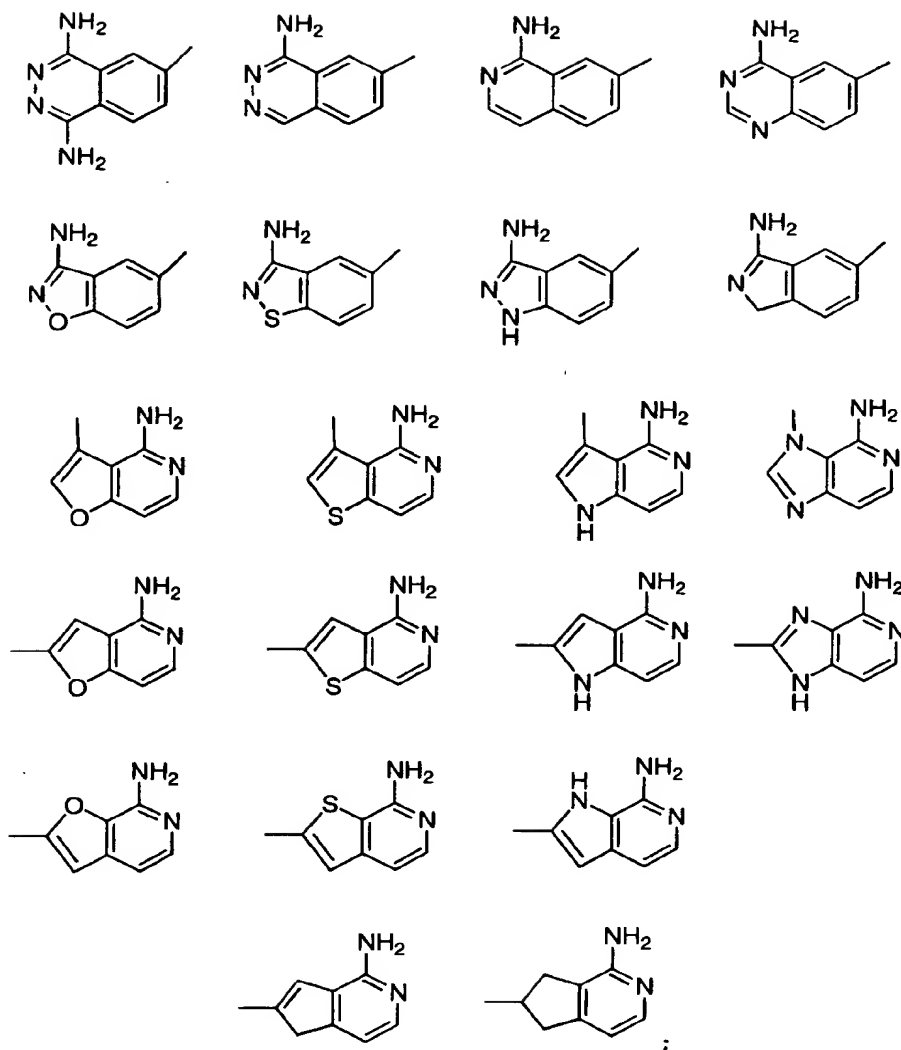
          u, at each occurrence, is selected from 0, 1, 2, and 3.  
40

5            2. A compound according to Claim 1, wherein:

G is selected from the group:



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A is 3-5 membered linker substituted with 0-2  $\text{R}^4$  and selected from  $\text{C}_{2-4}$  alkylene,  $(\text{CH}_2)_u\text{O}(\text{CH}_2)_u$ ,  $(\text{CH}_2)_u\text{NH}(\text{CH}_2)_u$ ,  $(\text{CH}_2)_u\text{C}(\text{O})(\text{CH}_2)_u$ ,  $(\text{CH}_2)_u\text{C}(\text{O})\text{O}(\text{CH}_2)_u$ ,  $(\text{CH}_2)_u\text{OC}(\text{O})(\text{CH}_2)_u$ ,  $(\text{CH}_2)_u\text{C}(\text{O})\text{NH}(\text{CH}_2)_u$ ,  $(\text{CH}_2)_u\text{NHC}(\text{O})(\text{CH}_2)_u$ ,  $(\text{CH}_2)_u\text{S}(\text{O})_p(\text{CH}_2)_u$ ,  $(\text{CH}_2)_u\text{SO}_2\text{NH}(\text{CH}_2)_u$ , and  $(\text{CH}_2)_u\text{NHSO}_2(\text{CH}_2)_u$ , provided that A forms other than a N-O or N-S bond;

15

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$\text{A}^1$  is 3-5 membered linker substituted with 0-2  $\text{R}^4$  and selected from  $\text{C}_{2-4}$  alkylene,  $(\text{CH}_2)_u\text{O}(\text{CH}_2)_u$ ,  $(\text{CH}_2)_u\text{NH}(\text{CH}_2)_u$ ,  $(\text{CH}_2)_u\text{C}(\text{O})(\text{CH}_2)_u$ ,  $(\text{CH}_2)_u\text{C}(\text{O})\text{O}(\text{CH}_2)_u$ ,  $(\text{CH}_2)_u\text{OC}(\text{O})(\text{CH}_2)_u$ ,  $(\text{CH}_2)_u\text{C}(\text{O})\text{NH}(\text{CH}_2)_u$ ,



- 5 (CH<sub>2</sub>)<sub>u</sub>NHC(O)(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>S(O)<sub>p</sub>(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>SO<sub>2</sub>NH(CH<sub>2</sub>)<sub>u</sub>,  
and (CH<sub>2</sub>)<sub>u</sub>NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>u</sub>, provided that A<sup>1</sup> forms other than  
a N-O or N-S bond;

alternatively, the CH<sub>2</sub>-A<sup>1</sup> group is replaced by a group  
10 selected from C=CH-NH and C=CH-O;

B is selected from: H, Y, X-Y;

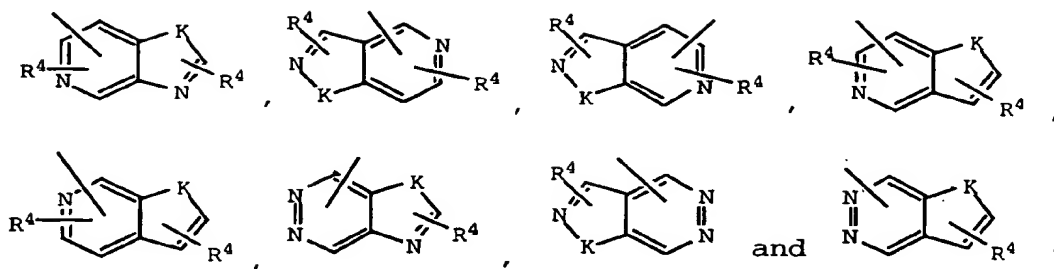
X is selected from C<sub>1-4</sub> alkylene, -C(O)-, -C(=NR)-,  
15 -CR<sup>2</sup>(NR<sup>2</sup>R<sup>2a</sup>)-, -C(O)CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>C(O)-, -C(O)NR<sup>2</sup>-,  
-NR<sup>2</sup>C(O)-, -C(O)NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -NR<sup>2</sup>C(O)CR<sup>2</sup>R<sup>2a</sup>-,  
-CR<sup>2</sup>R<sup>2a</sup>C(O)NR<sup>2</sup>-, -CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>C(O)-, -NR<sup>2</sup>C(O)NR<sup>2</sup>-, -NR<sup>2</sup>-,  
-NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>-, O, -CR<sup>2</sup>R<sup>2a</sup>O-, and -OCR<sup>2</sup>R<sup>2a</sup>-;

20 Y is NR<sup>2</sup>R<sup>2a</sup>, provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following  
carbocyclic and heterocyclic systems which are  
substituted with 0-2 R<sup>4a</sup>;

25 cyclopropyl, cyclopentyl, cyclohexyl, phenyl,  
piperidiny, piperaziny, pyridyl, pyrimidyl, furanyl,  
morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl,  
oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl,  
isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,  
30 thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,  
1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl,  
1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl,  
1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl,  
1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,  
35 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl,  
benzothiofuranyl, indolyl, benzimidazolyl,  
benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl,  
benzisothiazolyl, and isoindazolyl;

40 alternatively, Y is selected from the following bicyclic  
heteroaryl ring systems:



K is selected from O, S, NH, and N; and,

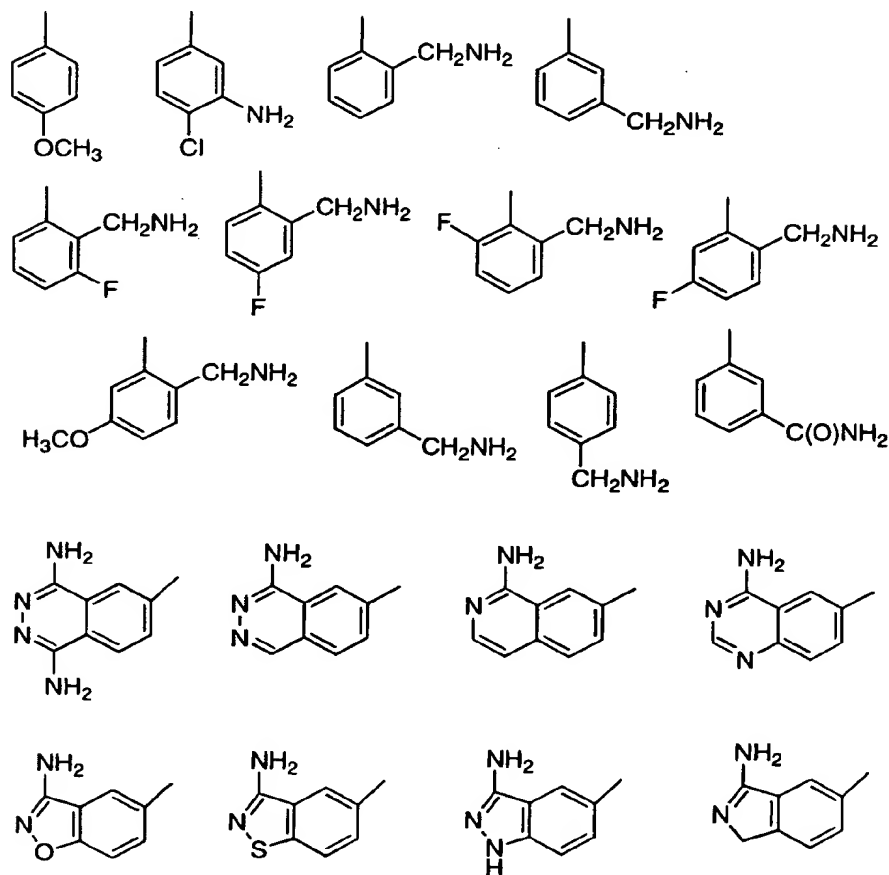
s is 0.

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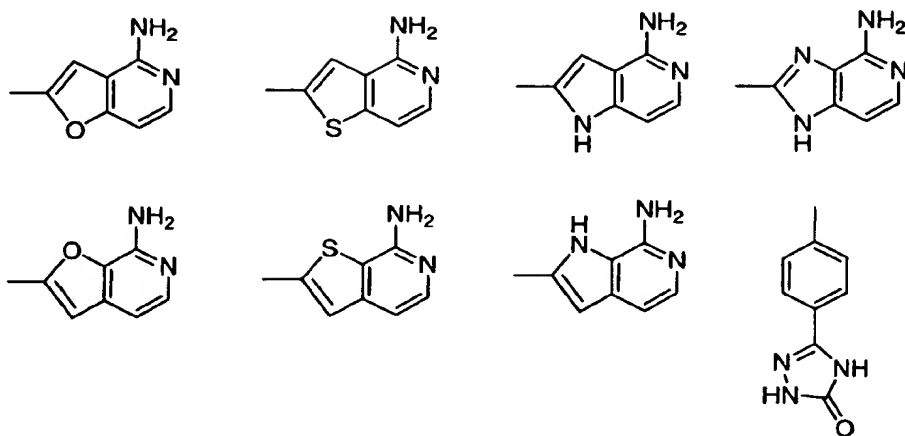
3. A compound according to Claim 2, wherein:

G is selected from the group:

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A is 3-5 membered linker substituted with 0-2  $R^4$  and selected from  $C_{2-4}$  alkylene,  $(CH_2)_uO(CH_2)_u$ ,  $(CH_2)_uNH(CH_2)_u$ ,  $(CH_2)_uC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)O(CH_2)_u$ ,  $(CH_2)_uOC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)NH(CH_2)_u$ ,  $(CH_2)_uNHC(O)(CH_2)_u$ ,  $(CH_2)_uSO_2NH(CH_2)_u$ , and  $(CH_2)_uNHSO_2(CH_2)_u$ , provided that A forms other than a N-O or N-S bond;

15

$A^1$  is 3-5 membered linker substituted with 0-2  $R^4$  and selected from  $C_{2-4}$  alkylene,  $(CH_2)_uO(CH_2)_u$ ,  $(CH_2)_uNH(CH_2)_u$ ,  $(CH_2)_uC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)NH(CH_2)_u$ ,  $(CH_2)_uNHC(O)(CH_2)_u$ ,  $(CH_2)_uSO_2NH(CH_2)_u$ , and  $(CH_2)_uNHSO_2(CH_2)_u$ , provided that  $A^1$  forms other than a N-O or N-S bond; and

20

alternatively, the  $CH_2-A^1$  group is replaced by a group selected from  $C=CH-NH$  and  $C=CH-O$ .

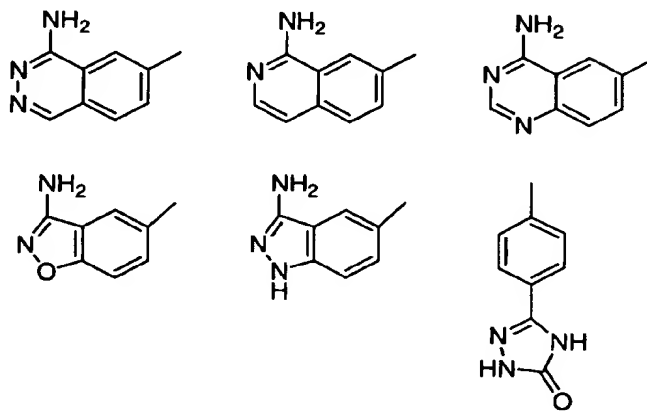
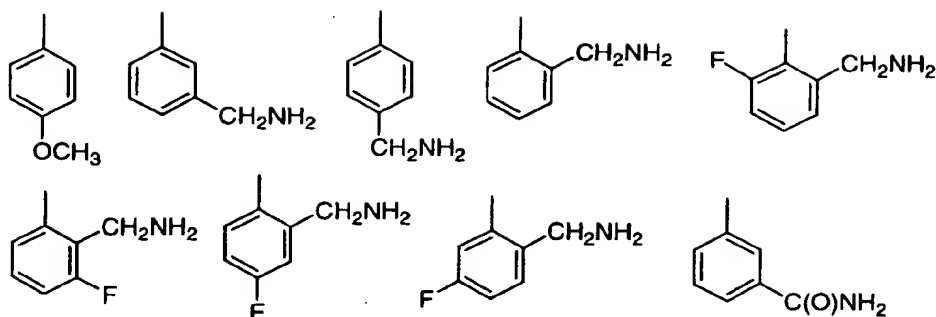
25

4. A compound according to Claim 3, wherein:

G is selected from:

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10 A is 3-5 membered linker substituted with 0-2  $R^4$  and selected from  $C_{2-4}$  alkylene,  $(CH_2)_uO(CH_2)_u$ ,  $(CH_2)_uNH(CH_2)_u$ ,  $(CH_2)_uC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)O(CH_2)_u$ , and  $(CH_2)_uOC(O)(CH_2)_u$ , provided that A forms other than a N-O or N-S bond;

15  $A^1$  is 3-5 membered linker substituted with 0-2  $R^4$  and selected from  $C_{2-4}$  alkylene,  $(CH_2)_uO(CH_2)_u$ ,  $(CH_2)_uNH(CH_2)_u$ ,  $(CH_2)_uC(O)(CH_2)_u$ ,  $(CH_2)_uC(O)NH(CH_2)_u$ ,  $(CH_2)_uNHC(O)(CH_2)_u$ ,  $(CH_2)_uSO_2NH(CH_2)_u$ , and  $(CH_2)_uNHSO_2(CH_2)_u$ , provided that  $A^1$  forms other than a N-O or N-S bond; and

alternatively, the  $CH_2-A^1$  group is replaced by a group selected from  $C=CH-NH$  and  $C=CH-O$ .

25

5. A compound according to Claim 4, wherein:

- 5 B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R<sup>4a</sup>;
- 10 R<sup>2</sup>, at each occurrence, is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, cyclopropylmethyl, cyclobutyl, and cyclopentyl;
- R<sup>2a</sup>, at each occurrence, is H or CH<sub>3</sub>;
- 15 alternatively, R<sup>2</sup> and R<sup>2a</sup>, together with the atom to which they are attached, combine to form pyrrolidine substituted with 0-2 R<sup>4b</sup>;
- 20 R<sup>4</sup>, at each occurrence, is selected from OH, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, halo, C<sub>1-4</sub> alkyl, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;
- R<sup>4a</sup> is selected from C<sub>1-4</sub> alkyl, CF<sub>3</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, S(O)<sub>p</sub>R<sup>5</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, and 1-CF<sub>3</sub>-tetrazol-2-yl;
- 25 R<sup>4b</sup>, at each occurrence, is selected from H, CH<sub>3</sub>, and OH;
- R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-6</sub> alkyl, phenyl, and benzyl;
- 30 A is 3-5 membered linker substituted with 0-2 R<sup>4</sup> and selected from C<sub>2-4</sub> alkylene, (CH<sub>2</sub>)<sub>u</sub>O(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>NH(CH<sub>2</sub>)<sub>u</sub>, and (CH<sub>2</sub>)<sub>u</sub>C(O)(CH<sub>2</sub>)<sub>u</sub>, provided that A forms other than a N-O or N-S bond;
- 35 A<sup>1</sup> is 3-5 membered linker substituted with 0-2 R<sup>4</sup> and selected from C<sub>2-4</sub> alkylene, (CH<sub>2</sub>)<sub>u</sub>O(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>NH(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>C(O)(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>C(O)NH(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>NHC(O)(CH<sub>2</sub>)<sub>u</sub>, (CH<sub>2</sub>)<sub>u</sub>SO<sub>2</sub>NH(CH<sub>2</sub>)<sub>u</sub>, and (CH<sub>2</sub>)<sub>u</sub>NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>u</sub>, provided that A<sup>1</sup> forms other than a N-
- 40 O or N-S bond; and

5 alternatively, the CH<sub>2</sub>-A<sup>1</sup> group is replaced by a group  
selected from C=CH-NH and C=CH-O.

X is CH<sub>2</sub> or C(O);

10 Y is selected from pyrrolidino and morpholino; and,  
r, at each occurrence, is selected from 0, 1, and 2.

15 6. A compound according to Claim 5, wherein:

B is selected from the group: 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 2-(N,N-  
20 dimethylaminomethyl)phenyl, 2-(N-pyrrolidinylmethyl)phenyl, 1-methyl-2-imidazolyl, 2-methyl-1-imidazolyl, 2-(dimethylaminomethyl)-1-imidazolyl, 2-(N-(cyclopropylmethyl)aminomethyl)phenyl, 2-(N-(cyclobutyl)aminomethyl)phenyl, 2-(N-(cyclopentyl)aminomethyl)phenyl, and 2-(N-(3-hydroxypyrrolidinyl)methyl)phenyl.  
25

30 7. A compound according to Claim 1, wherein the  
compound is selected from:

1-[[1-[3-(Aminomethyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole;  
35 1-[[1-[3-(Aminoiminomethyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole;  
40 1-[[1-[3-Cyano-4-fluorophenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole;  
45 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1H-indole;

- 5 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[2-  
(methysulfonyl)phenyl]-1H-indole;
- 10 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[2-(1-  
pyrrolidinylmethyl)phenyl]-1H-indole;
- 15 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[3-(1-  
pyrrolidinylmethyl)phenyl]-1H-indole;
- 20 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[(2'-  
dimethylaminomethyl)imidazol-1-yl]-indoline;
- 25 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-2,3,4,5-tetrahydro-7-[2-  
(aminosulfonyl)phenyl]-benzazepine;
- 30 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-6-[2-  
(methysulfonyl)phenyl]-1H-quinoline;
- 35 4-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-2,3-dihydro-7-[2-  
(methysulfonyl)phenyl]-2H-1,4-benzoxazine;
- 40 1-[[1-(3-Amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-4-[2-(methysulfonyl)phenyl]-  
3-indole;
- 45 5-[2-(aminosulfonyl)phenyl]-2,3-dihydro-1-[[1-(4-  
methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-  
yl]carbonyl]-1H-indole;
- 50 5-[2-(aminosulfonyl)phenyl]-1-[[1-(4-methoxyphenyl)-3-  
(trifluoromethyl)-1H-pyrazol-5-yl]carbonyl]-1H-indole;
- 55 1-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-6-[2-(aminosulfonyl)phenyl]-  
2,3-dihydro-4(1H)-quinolinone;
- 1-[[1-[3-(aminomethyl)phenyl]-3-(trifluoromethyl)-1H-  
pyrazol-5-yl]carbonyl]-2,3-dihydro-5-(1-  
pyrrolidinylcarbonyl)-1H-indole;
- 1-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-6-[2-(aminosulfonyl)phenyl]-  
1,2,3,4-tetrahydroquinoxaline;

- 5 1-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-7-[2-(aminosulfonyl)phenyl]-  
2,3,4,5-tetrahydro-1H-1-benzazepine;
- 10 1-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-7-[2-(aminosulfonyl)phenyl]-  
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine;
- 15 1-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-7-[2-(aminosulfonyl)phenyl]-  
2,3,4,5-tetrahydro-1H-1,4-benzodiazepine;
- 20 5-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-8-[2-(aminosulfonyl)phenyl]-  
1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one;
- 25 5-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-8-[2-(aminosulfonyl)phenyl]-  
1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one;
- 30 1-[[1-[3-(aminoiminomethyl)phenyl]-3-(trifluoromethyl)-1H-  
pyrazol-5-yl]carbonyl]-5-[2-(aminosulfonyl)phenyl]-2,3-  
dihydro-1H-indole;
- 35 [1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-  
pyrazol-5-yl][6-[2-[(dimethylamino)methyl]phenyl]-2,3-  
dihydro-1-methyl-1H-indol-3-yl]methanone;
- 40 5-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-8-[2-(aminosulfonyl)phenyl]-  
2,3,4,5-tetrahydro-1,5-benzoxazepine;
- 45 1-[[1-[3-(aminoiminomethyl)phenyl]-3-(trifluoromethyl)-1H-  
pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[2-  
(methylsulfonyl)phenyl]-1H-indole;
- 50 [1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-  
pyrazol-5-yl][6-[2-[(dimethylamino)methyl]phenyl]-2,3-  
dihydro-1H-indol-3-yl]methanone;
- 55 1-[[1-[3-(aminoiminomethyl)phenyl]-3-(trifluoromethyl)-1H-  
pyrazol-5-yl]carbonyl]-7-[2-(aminosulfonyl)phenyl]-  
1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one;
- 60 1-[[1-[3-(aminoiminomethyl)phenyl]-3-(trifluoromethyl)-1H-  
pyrazol-5-yl]carbonyl]-2,3-dihydro-5-[2-(1-  
pyrrolidinylmethyl)phenyl]-1H-indole;
- 1-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-  
pyrazol-5-yl][2,3-dihydro-6-[2-(methylsulfonyl)phenyl]-  
1H-indol-3-yl]methanone;
- 1-[[1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-  
1H-pyrazol-5-yl]carbonyl]-7-[2-(aminosulfonyl)phenyl]-  
1,2,3,5-tetrahydro-4,1-benzoxazepine;



- 5 1-[[1-[3-(aminoiminomethyl)phenyl]-3-(trifluoromethyl)-1H-  
pyrazol-5-yl]carbonyl]-5-[2-  
[(dimethylamino)methyl]phenyl]-2,3-dihydro-1H-indole;
- 10 1-[[1-(1-amino-7-isoquinoliny)-3-(trifluoromethyl)-1H-  
pyrazol-5-yl]carbonyl]-5-[2-  
[(dimethylamino)methyl]phenyl]-2,3-dihydro-1H-indole;
- 15 [1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-  
pyrazol-5-yl][6-[2-[(dimethylamino)methyl]phenyl]-1H-  
indol-3-yl]methanone;
- 20 [1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-  
pyrazol-5-yl][6-[2-[(dimethylamino)methyl]phenyl]-1-  
methyl-1H-indol-3-yl]methanone; and,
- 25 [1-(3-amino-1,2-benzisoxazol-5-yl)-3-(trifluoromethyl)-1H-  
pyrazol-5-yl][6-[2-[(dimethylamino)methyl]phenyl]-3-  
benzofuranyl]methanone;
- or a pharmaceutically acceptable salt form thereof.

8. A pharmaceutical compositions, comprising: a  
pharmaceutically acceptable carrier and a therapeutically  
30 effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, or  
7 or a pharmaceutically acceptable salt form thereof.

9. A method for treating or preventing a  
35 thromboembolic disorder, comprising: administering to a  
patient in need thereof a therapeutically effective amount  
of a compound of Claim 1, 2, 3, 4, 5, 6, or 7 or a  
pharmaceutically acceptable salt form thereof.

40

10. A compound of Claim 1, 2, 3, 4, 5, 6, or 7 for use  
in therapy.

45 11. Use of compound of Claim 1, 2, 3, 4, 5, 6, or 7  
for the manufacture of a medicament for the treatment of a  
thromboembolic disorder.

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/18903

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/06 A61K31/33 A61P7/02 C07D413/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 57951 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 23 December 1998 (1998-12-23) cited in the application page 4, line 18 - line 21; claims -----	1,8,11
A	WO 98 28269 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 2 July 1998 (1998-07-02) cited in the application page 3, line 19 - line 22; claims -----	1,8,11

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Van Bijlen, H

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter? Final Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9857951 A	23-12-1998	AU 7976898 A	04-01-1999
		BR 9810137 A	08-08-2000
		CN 1259942 T	12-07-2000
		EP 0991638 A	12-04-2000
		HR 980333 A	28-02-1999
		LT 99147 A, B	25-04-2000
		LV 12496 A	20-06-2000
		NO 995965 A	03-12-1999
		PL 337756 A	11-09-2000
		SI 20160 A	31-08-2000
		SK 172899 A	12-06-2000
WO 9828269 A	02-07-1998	AU 5602098 A	17-07-1998
		CN 1246847 A	08-03-2000
		EP 0946508 A	06-10-1999
		HR 970698 A	31-10-1998
		LT 99076 A, B	25-02-2000
		LV 12430 A	20-02-2000
		LV 12430 B	20-07-2000
		NO 992633 A	20-08-1999
		PL 334250 A	14-02-2000
		SI 20017 A	29-02-2000
		US 6020357 A	01-02-2000
		BR 9714073 A	09-05-2000

